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SULTONE CHEMISTRY

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CONTENTS

1. NOMENCLATURE

Sultones are the internal esters of hydroxy sulphonic acids and are the sulphur analogues of the lactones. Many sultones with 4 to 6-membered rings are known, as well as a small number with 7-membered rings. Figure 1 shows some representative structures.

The term "sultone" was introduced into the literature by Erdmann[1] in 1888 and subsequently several types of nomenclature have been adopted.[2,3] Since sultones are internal esters they have been named from the appropriate β-, γ- or δ-hydroxy sulphonic acid.[3] Thus **1** and **2** have been known as butane γ- and butane δ-hydroxy sulphonic acid sultones respectively, or more simply as butane γ- and δ-sultones.

A more precise nomenclature, since adopted for aliphatic sultones, numbers the carbon bearing the sulphur atom followed by the carbon bearing the oxygen atom, naming the longest carbon chain

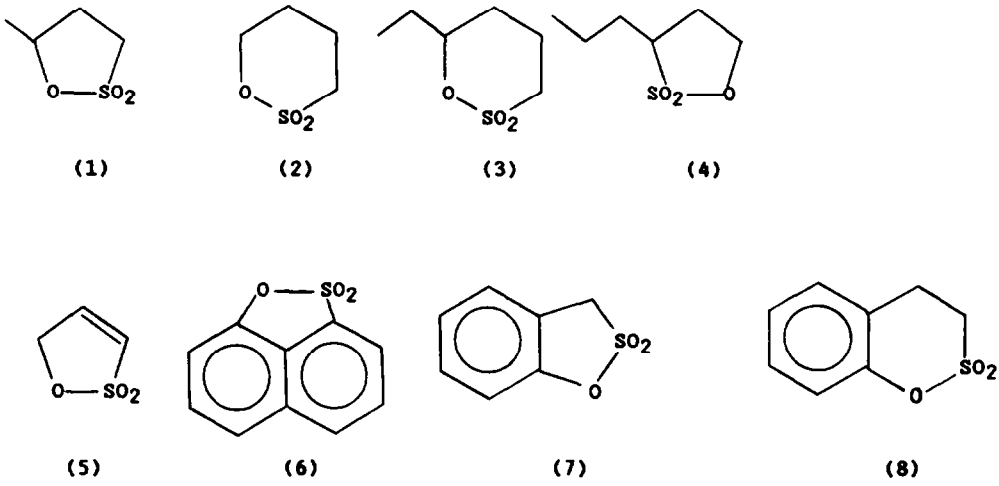


Fig. 1. Representative sultone structures.

containing these two carbon atoms. Thus **3** and **4** may be named hexane-1,4-sultone and hexane-3,1-sultone, respectively, and **5** may be named 1-propene-1,3-sultone.

Both types of nomenclature have their advantages. In this report, preferring clarity to uniformity, we have chosen on each occasion the type of nomenclature which seems more suitable to the context.

In the systematic nomenclature, for the most part not used in this report, 5 and 6 membered ring aliphatic sultones are named as the appropriately substituted 1,2-oxathiolane-2,2-dioxide and 1,2-oxathiin-2,2-dioxide respectively and **5** is named as 1,2-oxathiole-2,2-dioxide.

Sultones in which the sultone ring is fused to an aromatic system (aromatic sultones) are also well known and are usually named from the appropriate aromatic system. Thus **6** and **7** are known as 1-hydroxynaphthalene-8-sulphonic acid sultone and *o*-hydroxy-α-toluenesulphonic acid sultone respectively, although the systematic nomenclature has also been adopted, e.g. **8** 1,2-benzoxathiin-2,2-dioxide.

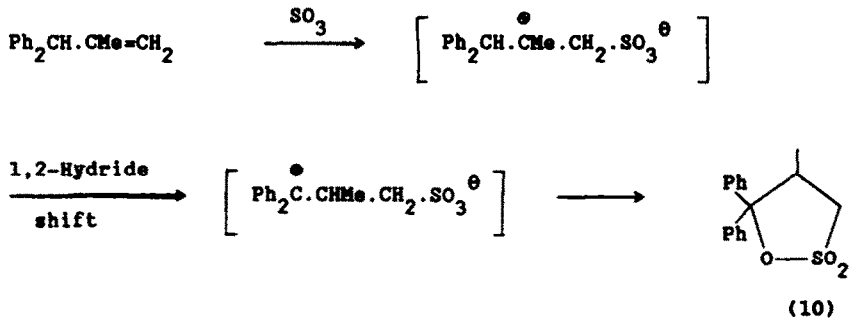
2. PREPARATION OF SULTONES

2.1. *Preparation of aliphatic saturated sultones*

2.1.1. *Cyclisation of hydroxysulphonic acids and their analogues.* Classical esterification methods used for the preparation of carboxylic acid esters from the alcohol and acid are, in general, not applicable to the preparation of sulphonic acid esters. Neither can sultones be prepared by acidification of hydroxy sulphonic acids (*cf* lactones from hydroxy carboxylic acids). The methods of preparation of sultones were reviewed by Mustafa[4] and Willems[5,6] in 1954 and 1955. The early methods were dominated by the direct distillation of the halogeno or hydroxy sulphonic acids under vacuum, splitting off the elements of hydrogen halide or water respectively and distilling the low molecular weight sultone in the process[7-9] (e.g. Eq. 1).

(1)

These methods have been widely adopted for unambiguously preparing relatively simple aliphatic γ- and δ-sultones, and, together with the preparation of the starting hydroxy sulphonic acids, form the basis of an extensive patent literature.[10-14] The 7-membered ring compound pentane-1,5 sultone has also been made in this way, by dehydration of 5-hydroxypentane sulphonic acid.[6]



Scheme 1. Sulphonation of 2-methyl-3,3-diphenyl-1-propene.[23]

Related methods are the preparation of sultones by heating acyloxysulphonic acids[15] and the preparation of butane-1,4-sultone (**2**) in 72–80% yield by heating bis(butane-4-sulphonic acid) ether with acid, this ether being prepared from bis-4-chlorobutyl ether and sodium sulphite.[16,17]

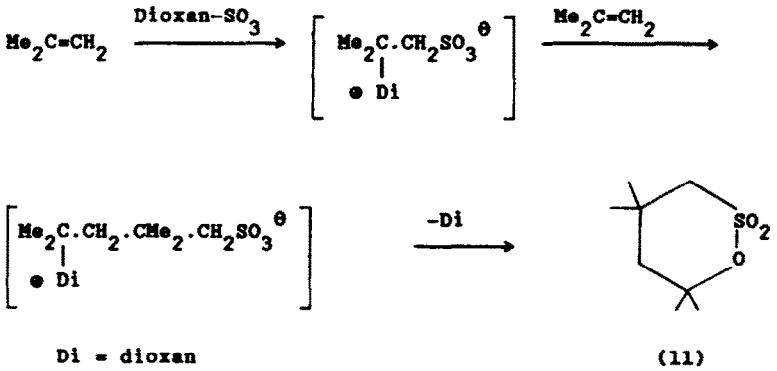
2.1.2. *Sulphonation of olefins.* During their mechanistic study of the sulphonation of alkenes with dioxan-sulphur trioxide complexes in the 1940s and 1950s, Bordwell *et al.*[18–29] prepared many γ- and δ-sultones from a variety of olefins. On sulphonation of a sample of 2-methyl-3,3-diphenyl-2-propene believed to contain 2-methyl-3,3-diphenyl-1-propene as an impurity, a small quantity of 3,3-diphenyl-2-methyl propane-1,3-sultone (**10**) was formed, presumably via the mechanism shown in Scheme 1.[23] Sulphonation of isobutene, however, was found to proceed by a dimerisation-sulphonation mechanism.[25] When a 1 : 1 dioxan-sulphur trioxide complex in methylene chloride at −60°C was treated with a 10 molar excess of isobutene and left for 24 hr at −60°C then for 48 hr at −10°C a 31% yield of 2,2,4-trimethyl pentane-1,4-sultone (**11**) was obtained. The proposed mechanism is shown in Scheme 2.

Sulphonation of highly branched alkenes[25] led to the formation of 1,3-sultones; rearrangement of intermediate dioxan-solvated secondary carbocations via a methide shift probably occurs, giving more stable tertiary carbocations which then cyclise to give the final sultones. Thus sulphonation of 3,3-dimethyl-1-butene at 0°C in methylene chloride with a molar equivalent of a 1 : 1 dioxan-sulphur trioxide complex gave a 71% yield of 2,3-dimethylbutane-1,3-sultone (**12**) as shown in Scheme 3.

Table 1 summarises the sultones which have been prepared by the dioxan-sulphur trioxide routes developed by Bordwell *et al.*[19,20,23,25,27–29]

Preparation of sultones from alkene sulphonation is also the subject of several patents to Henkel & Cie, G.m.b.H.[30]

Although the dioxan sulphur trioxide complex is the most common reagent for sulphonation, complexes with other Lewis bases have also been used, amongst the most popular being pyridine-sulphur trioxide, first introduced by Terent'ev *et al.* in 1959.[31] Since then a wide range of ethers and

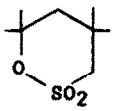
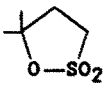
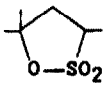
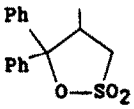
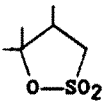
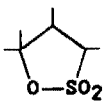
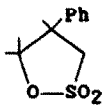
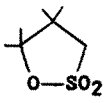
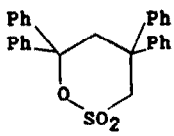
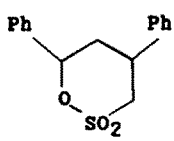


Scheme 2. Sulphonation of isobutene.[25]

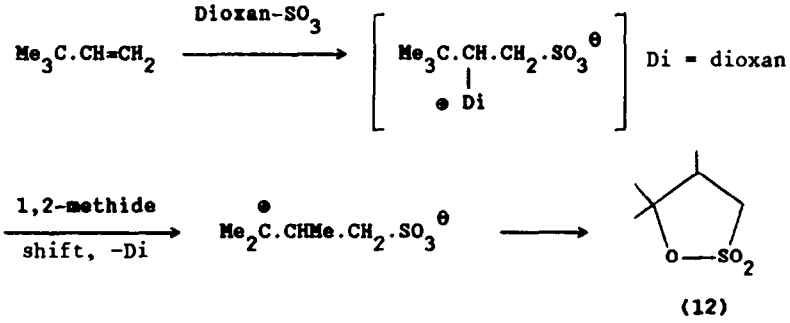
amines have been investigated; most of these complexes have the advantages of being adequately reactive towards organic substrates whilst offering substantial reduction in charring of products which usually occurs with uncomplexed sulphur trioxide. The disadvantages of complexed sulphur trioxide, however, are that yields are often quite low and side reactions may occur as a result of stabilisation of intermediates by the complexing agent.

An alternative approach to moderating the high reactivity of sulphur trioxide is to use low concentration and low reaction temperatures. Thus in sulphonation of alkenes with uncomplexed

Table 1. Sultones prepared from alkenes by the dioxan-SO_3 route

Alkene	Ref	Sultone	Sultone number	Yield	Proposed mechanism
$Me_2C{=}CH_2$	25		11	31%	Dimerisation -sulphonation
$Me_2CH.CH{=}CH_2$	25		13	53%	Hydride shift
$Me_2CH.CH{=}CHMe$	25		14	82%	Hydride shift
$Ph_2CH.CMe{=}CH_2$	23		10	Not found[a]	Hydride shift
$Ph_2C{=}CMe_2$	23	None	—	—	—
$Me_3C.CH{=}CH_2$	25		12	71%	Methide shift
$Me_3C.CH{=}CHMe$	25		15	51%	Methide shift
$Me_3C.CPh{=}CH_2$	25		16	73%	Methide shift
$Me_3C.CMe{=}CH_2$	25		17	76%	Methide shift
$Ph_2C{=}CH_2$	28		18	10%	Dimerisation
$PhCH{=}CH_2$	19, 20, 27, 29		19	ca. 10%	Dimerisation

[a] Sultone **10** (characterised by elemental analysis only) was formed as a by-product (*ca* 5%) of the sulphonation of the olefin $Ph_2C{=}CMe_2$, which was assumed to contain the olefin $Ph_2CH.CMe{=}CH_2$ as an impurity.

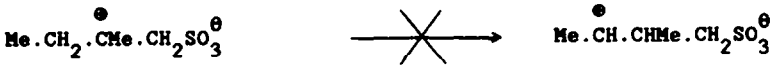


(12)

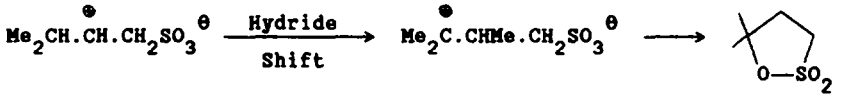
Scheme 3. Sulphonation of 3,3-dimethyl-1-butene.[25]

sulphur trioxide in dichloromethane at −78° with 0.1 M concentrations Robbins and Broaddus[32] obtained alkane 1,3-sultones in yields of at least 75% with very little of the 2-alkene-1-sulphonic acids, which are usually major by-products. Table 2 shows the yields of 1,3-sultone from various 1-butenes.

It is clear from these studies and from the work of Bordwell *et al.* that the controlling factor in sultone vs sulphonic acid formation is the relative stability of the carbocation formed at the β and γ carbons. For example, 2-methyl-1-butene yields no sultone since the tertiary β-carbocation cannot cyclise and does not undergo a 1,2-hydride shift.



3-Methyl-1-butene on the other hand can yield a 1,3-sultone since the initially formed secondary carbocation is readily converted into a more stable γ carbocation which can cyclise (Eq. 2).



(2)

(13)

Broaddus and Robbins[32] state that in unpublished work they have also prepared 1,4-sultones from suitable 1-pentenes, i.e. where the δ-carbocation is more stable than the γ-carbocation.

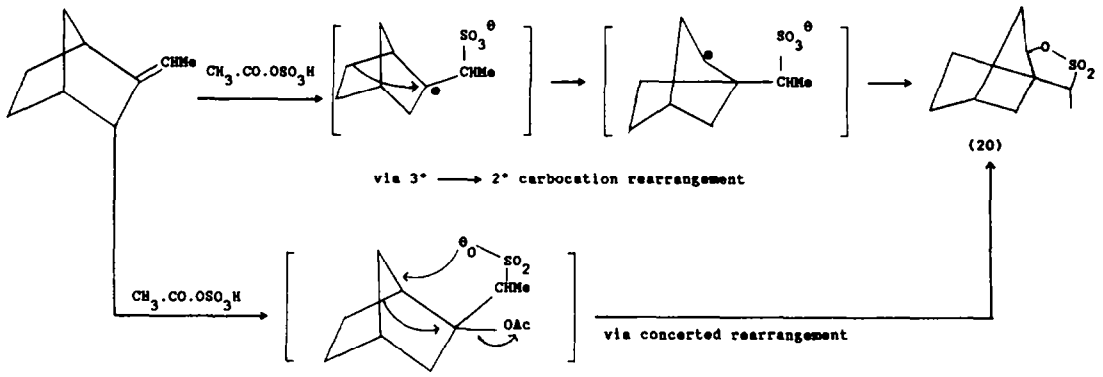
A case where formation of a γ-sultone (**20**) appears to involve rearrangement of a tertiary β-carbocation to a secondary carbocation is provided by the sulphonation of ethylidene norbornane by acetyl sulphate,[33] as shown in Scheme 4.

However, a concerted mechanism with rearrangement accompanying displacement of an intermediate tertiary acetate, as shown in the lower part of Scheme 4, cannot be excluded.

Olefin sulphonation has also been used to prepare β-sultones, in cases where they are stable

Table 2. Yields of sultones and substituted 2-butenesulphonic acids from substituted 1-butenes and sulphur trioxide[32]

	Product ratio		
Butene	1,3-Sultone	Substituted 2-butene-1-sulphonic acid	Absolute yield of sultone
1-Butene	87	13	78
2-Methyl-1-butene	0	100	0
3-Methyl-1-butene	89	11	65
2,3-Dimethyl-1-butene	90	10	72
3,3-Dimethyl-1-butene	100	0	83
2,3,3-Trimethyl-1-butene	100	0	98



Scheme 4. Formation of a γ-sultone from sulphonation of ethylidene norbornane by acetyl sulphate.[33]

enough to be isolated. Thus, Bordwell *et al.* isolated a β-sultone (2-phenylethane-1,2-sultone, **21**) by low temperature extraction from a styrene sulphonation reaction mixture; this sultone was found to be too unstable to be stored at room temperature, decomposing to 2-phenylethylene sulphonic acid.[20]

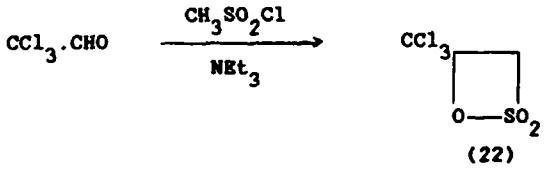
β-Sultones bearing highly electronegative substituents in the ring can, in many cases, be isolated in good yields from sulphonation of the corresponding olefins. England *et al.*[34] describe the preparation of several fluorine-substituted sultones from the corresponding fluoro-olefins. Fluorinated β-sultones are the subject of an excellent 1972 review by Knunyants and Sokolski,[35] who have also produced an extensive number of papers on the subject since 1957 when the first fluorinated β-sultone was identified. They found that increasing the number of fluorine substituents around the ring increases the stability of the β-sultone. Sulphonation of fluoro olefins normally requires uncomplexed sulphur trioxide, the temperature required increasing with increasing fluorine content. Olefins bearing chloro substituents require still higher temperatures for sulphonation, as illustrated by the following data taken from Knunyants and Sokolski.[35]

Olefin	β-Sultone Isolated	Optimum Sulphonation Temperature
$CH_2{=}CHF$	No	−30°
$CH_2{=}CF_2$	No	0°
$CHF{=}CF_2$	Yes	20–30°
$CF_2{=}CF_2$	Yes	40–50°
$CCl_2{=}CF_2$	Yes	80°
$CFCl{=}CFCl$	Yes	80°
$CCl_2{=}CFCl$	No	160–180°
$CCl_2{=}CCl_2$	No	180–200°

The formation of β-sultones from fluoro-olefin sulphonation tends to be highly regiospecific. Electronic effects outweigh steric effects, resulting in exclusive formation of the isomer with oxygen bonded to the carbon atom whose substituents are best able to stabilise a positive charge. Thus the following olefins give β-sultones with the sulphur atom bonded to the carbon atom underlined: $\underline{C}HF{=}CF_2$,[35] $\underline{C}Cl_2{=}CF_2$,[35] $CF_2{=}\underline{C}FCF_3$,[35] $\underline{C}F_2{=}C(CF_3)OEt$,[36] $\underline{C}F_2{=}CFOC_3F_7$.[36] An exception appears to be chlorotrifluorethylene, which is reported to give an approximately equimolar mixture of the two possible β-sultones.[34]

β-Sultones substituted in the β-position by one or two perhalomethyl groups are also sufficiently stable to be isolated.[37] They have been prepared by the reaction of mesyl chloride in the presence of triethylamine with trihaloaldehydes or perhaloketones, as exemplified by Eqs 3 and 4.

2.1.3. *Halogenation of unsaturated sulphonates.* Salts of unsaturated sulphonic acids, obtained from sulphonation of alkenes can react with sources of positive halogen to give halogenated γ- or δ-sultones, in a reaction ("halosultonisation") analogous to the well known halolactonisation reactions of unsaturated carboxylic acids and their salts. Thus, Bordwell *et al.*[18] obtained 2-bromo-2-



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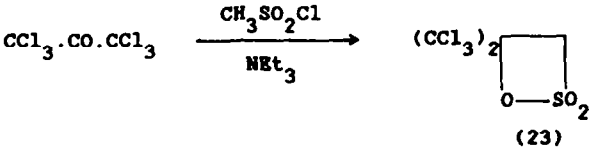
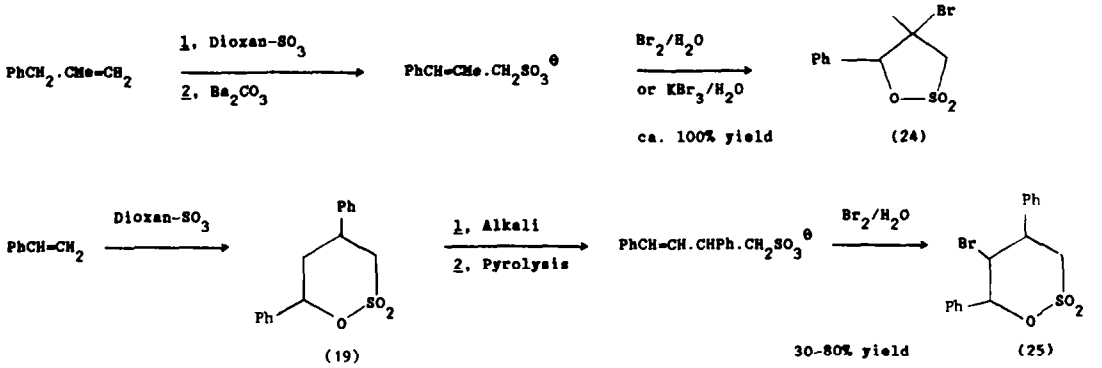


(4)

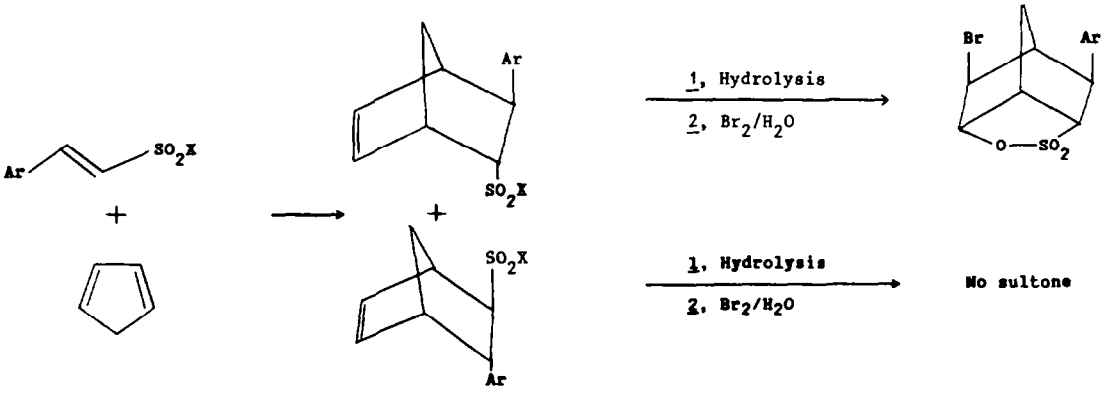
methyl-3-phenylpropane-1,3-sultone (**24**) by bromination of the neutralised sulphonation product from 2-benzyl-1-propene and Bordwell *et al.*[27] prepared 3-bromo-2,4-diphenylbutane-1,4-sultone (**25**) from 2,4-diphenyl-3-butene-1-sulphonate (Scheme 5). In the latter case the corresponding chlorosultone was also obtained, using chlorine in place of bromine.

Rondestvedt and Wygant[38] have used the halosultonisation reaction to distinguish between the stereoisomers produced from the Diels–Alder reactions between cyclopentadiene and trans-2-arylethylenesulphonic acid derivatives (Scheme 6).

2.1.4. *Metallation of alkane sulphonate esters.* Durst and Tin[39] have developed an unambiguous route to γ- and δ-sultones from alkane sulphonate esters of alcohols with a leaving group X in the β or γ position, respectively. Treatment with a molar equivalent of n-butyl lithium in tetrahydrofuran at $-78°$ leads to formation of the lithiated species (**26**) which yields the sultone by intramolecular

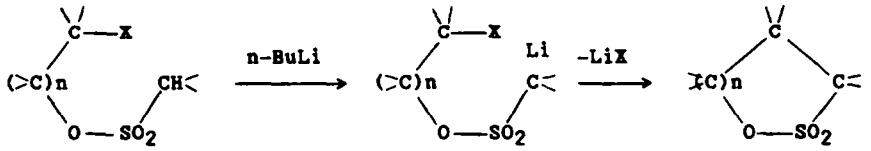


Scheme 5. Halosultonisation reactions.[18,27]



Scheme 6. Use of the halosultonisation reaction for assignment of stereochemistry.[38]

displacement:



Di-methanesulphonate esters of unsymmetrical diols cyclise with displacement occurring mainly at the least substituted carbon atom (Scheme 7).

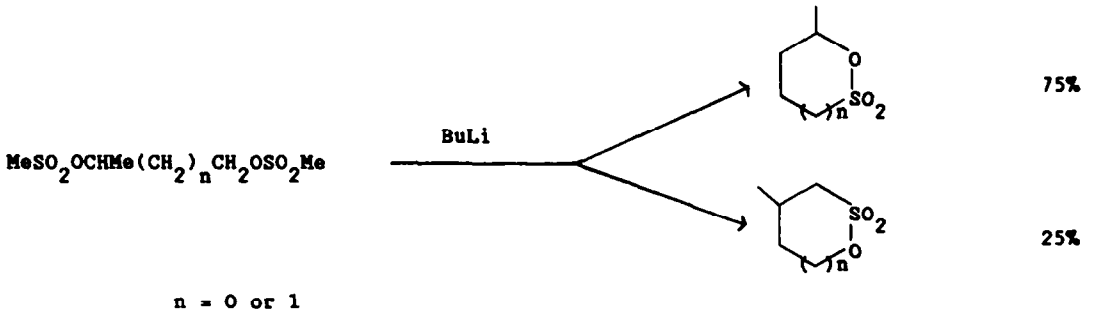
This route can be used to prepare 1,3-sultones from the haloalkanesulphonate esters derived from 1,2-halohydrins, although the yields are lower than those obtained when X is alkane sulphonate, since the effectiveness of the leaving group X decreases in the order $-OSO_2CH_3 >$ Br > Cl. An attraction of this route is the availability of 1,2-halohydrins and 1,2-diols of known stereochemistry, which can lead to the formation of sultones having uniquely defined stereochemistry as exemplified in Scheme 8.

Formation of 7-membered ring sultones by this route was attempted, but without success.[39]

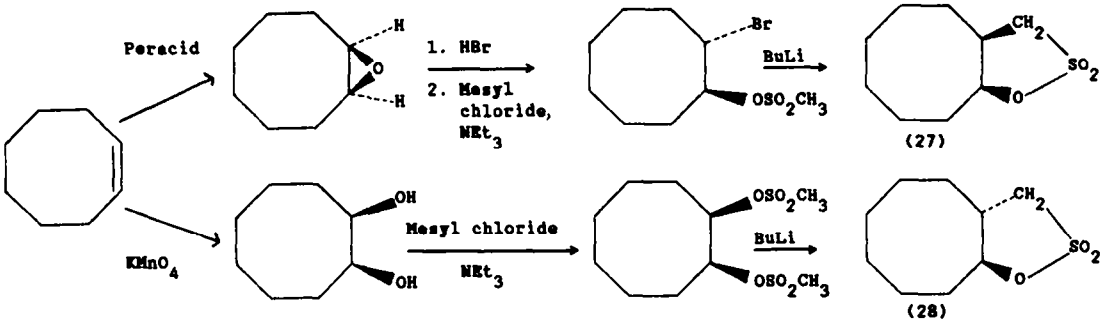
2.1.5. *Oxidation of* 1,2-*oxathiole.* Preparation of propane-1,3-sultone (**29**) has also been achieved by pyrolysis of N-(3-hydroxypropylthio)phthalimide,[40] followed by oxidation of the resultant 1,2-oxathiole with 2 mole equivalents of *m*-chloroperbenzoic acid (Scheme 9).

2.1.6. *The role of β-sultones in olefin sulphonation.* Sulphonation of olefins is usually depicted as proceeding via a β-zwitterion, as in the examples presented in Section 2.1.2. β-Sultones have been detected as early reaction products in sulphonation of several alkanes but, with a few exceptions (see Section 2.1.2), they tend to be too unstable to be isolated and fully characterised.

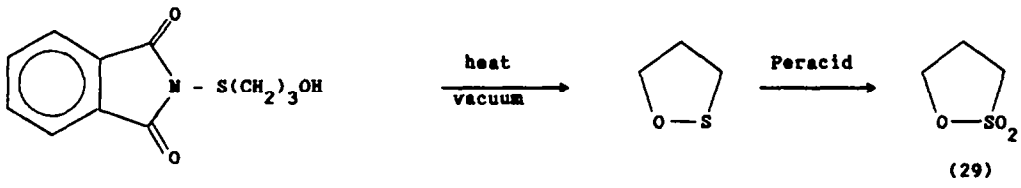
Direct evidence for their presence in reaction mixtures from sulphonation of olefins of the types $R.CH{=}CH_2$ and R.CH=CH.R (R = unbranched alkyl) comes from their detection by NMR and from experiments in which treatment with nucleophiles leads to formation of the corresponding β-substituted sulphonates (see later, Section 3.1.2) which can be isolated and fully characterised.[41-44]



Scheme 7. Sultones from metallation of di-methanesulphonate esters of unsymmetrical diols.[39]



Scheme 8. Stereospecific synthesis of sultones by the metallation route.[39]



(29)

Scheme 9. Propane-1,3-sultone synthesis via 1,2-oxathiole.[40]

Until recently it has been widely assumed that the initial step in olefin sulphonation is formation of the β-zwitterion, which may either ring close reversibly to form the β-sultone or undergo rearrangement or proton elimination reactions. Consistent with this interpretation has been the absence of evidence for the existence of tertiary β-sultones, i.e. β-sultones with two alkyl groups at the β-position, corresponding to β-zwitterions in which the carbocationic centre is tertiary. Thus, Mori *et al.* found that addition of aniline to the sulphonation product of 2-methyl-1-undecene gave only anilinium salts of alkene sulphonic acids, and neutralisation of the 2-methyl-1-undecene sulphonation product gave no β-hydroxy sulphonates (or any other hydroxy sulphonates).[42] It should be noted however that Mori *et al.* do not themselves interpret these findings as evidence against the participation of a β-sultone, but simply conclude that the tertiary β-sultone or the β-zwitterion decomposes too rapidly to be trapped. In recent work from our laboratory, tertiary β-sultones have been identified, by ^{1}H and ^{13}C NMR, as major products from sulphonation of isobutene, trimethylethylene and tetramethylethylene at −50°C and below.[45]

Perhaps the strongest evidence in favour of the β-zwitterion as the initial product comes from a kinetic and analytical study by Boyer *et al.*,[44] who sulphonated 1-hexene with a sulphur trioxide-dioxan complex in dichloroethane. These workers followed the rate of β-sultone decomposition (by GLC analysis for methyl 2-methoxyhexanesulphonate formed from the β-sultone after quenching with methanol and methylation with diazomethane) and also determined the levels of alkenesulphonic acids (analysed by GLC as their methyl esters) at the start of the kinetic run. The observed ratio of β-sultone to alkenesulphonic acid (5.9) is much lower than the value calculated (690) from the rate constant for β-sultone decomposition and the time interval which had elapsed after addition of the sulphonating agent to the 1-hexene. This suggests that the alkenesulphonic acid did not originate solely from the β-sultone, but was formed from an earlier intermediate, whose most plausible identity is that of the β-zwitterion. However, since it is known that in the case of reaction mixtures from sulphonation by free sulphur trioxide the β-sultone decomposition undergoes acid catalysis,[46] it seems possible that in the case of sulphonation by the sulphur trioxide-dioxan complex the β-sultone would decompose much more readily during the sulphonation reaction, due to catalysis by the sulphur trioxide, than subsequently when no sulphur trioxide remained.

Evidence that β-sultones are formed directly rather than *via* β-zwitterions is provided by the observations of Mori *et al.*, published in the early 1970s, that sulphonation of *cis*-2-butene gives the *cis*-butane-2,3-sultone whilst sulphonation of *trans*-2-butene gives *trans*-butane-2,3-sultone.[47,48] The implications of these findings were largely ignored for several years, but have recently been supported by relative reactivity studies on sulphonation of mono, di and tri-alkyl substituted ethylenes with sulphur trioxide.[49]

The results, summarised in Table 3, indicate that the spread of reactivities is only a factor of 3.4, even though some of the corresponding β-zwitterions would only be secondary whilst others would be tertiary. This seems incompatible with the β-zwitterions as the initial products, but is consistent with a concerted cycloaddition reaction to form the β-sultones directly. Orbital correlation analysis reveals that for olefin sulphonation the concerted $[2_s+2_s]$ cycloaddition reaction is thermally allowed and, since the relative reactivity pattern is not consistent with the $[2_s+2_a]$ mode of cycloaddition (for which olefin **32** should react much faster than olefins **33** or **34** and olefin **35** should react much faster than olefin **38**) it has been argued that the $[2_s+2_a]$ pathway applies.[49]

2.2. *Preparation of unsaturated aliphatic sultones*

2.2.1. *δ-Sultones.* Sulphonation of conjugated dienes can give rise to β-unsaturated δ-sultones.[50,51] Yields vary considerably with diene structure, as illustrated in Table 4. A related

Table 3. Relative rates for olefin sulphonation at −50° with sulphur trioxide in dichloromethane[49]

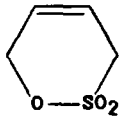
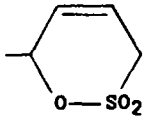
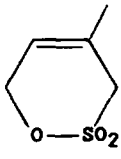
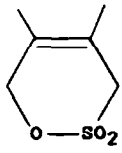
	Olefin	k_{rel}
30	$Me(CH_2)_6CH{=}CH_2$	0.59
31	$Me_3CCH{=}CMe_2$	0.65
32	$Me(CH_2)_2CH{=}CH(CH_2)_2Me$ cis	0.71
33	$Me(CH_2)_2CH{=}CH(CH_2)_2Me$ trans	0.71
34	$Me(CH_2)_4CH{=}CHMe$ trans	0.71
35	*Z*-$MeCH_2C(Me){=}CHMe$	0.88
36	$Me(CH_2)_3C(Et){=}CH_2$	1.00
37	$Me_3CCH_2C(Me){=}CH_2$	1.00
38	*E*-$MeCH_2C(Me){=}CHMe$	2.00

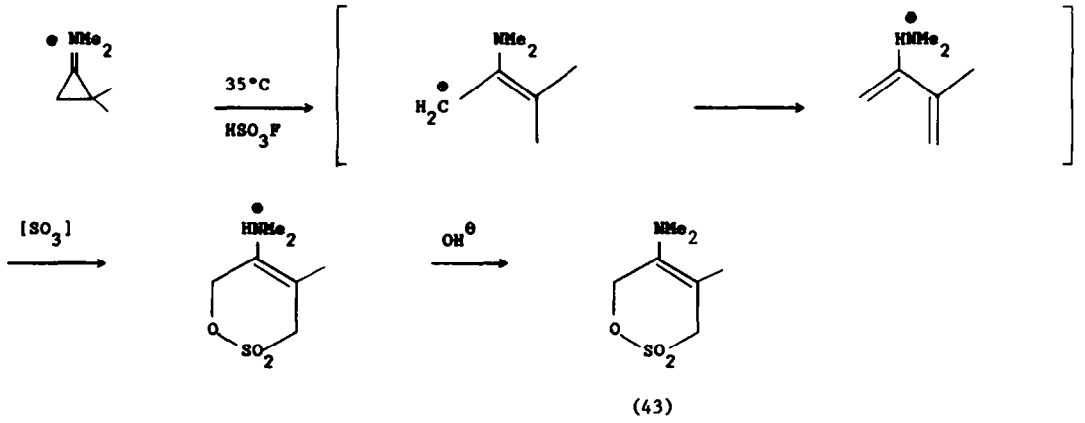
synthesis is that of 2-methyl-3-dimethylamino-2-butene-1,4-sultone (**43**) by reaction of *N*,*N*-dimethyl-2,2-dimethyl cyclopropaniminium ion with fluorosulphonic acid, for which the mechanism shown in Scheme 10 has been proposed.[52]

α,γ-Di-unsaturated δ-sultones (1,2-oxathiin-2,2-dioxides) have been prepared by sulphonation reactions[3,53,54] and also by a bromination/dehydrobromination sequence[50] starting from 2-methyl-2-butene-1,4-sultone (**41**), as shown in Scheme 11. The unsaturated ketone sulphonation route is not applicable to sultones which are not substituted in the β and δ positions. Spectroscopic[54] and x-ray crystallographic[55] studies indicate that the α-γ-diunsaturated-δ-sultone ring system (1,2-oxathiin-2,2-dioxide) has little, if any, aromatic character.

3-Bromo-2-methyl-1-butene-1,4-sultone (**44**), which is an intermediate in the bromination/

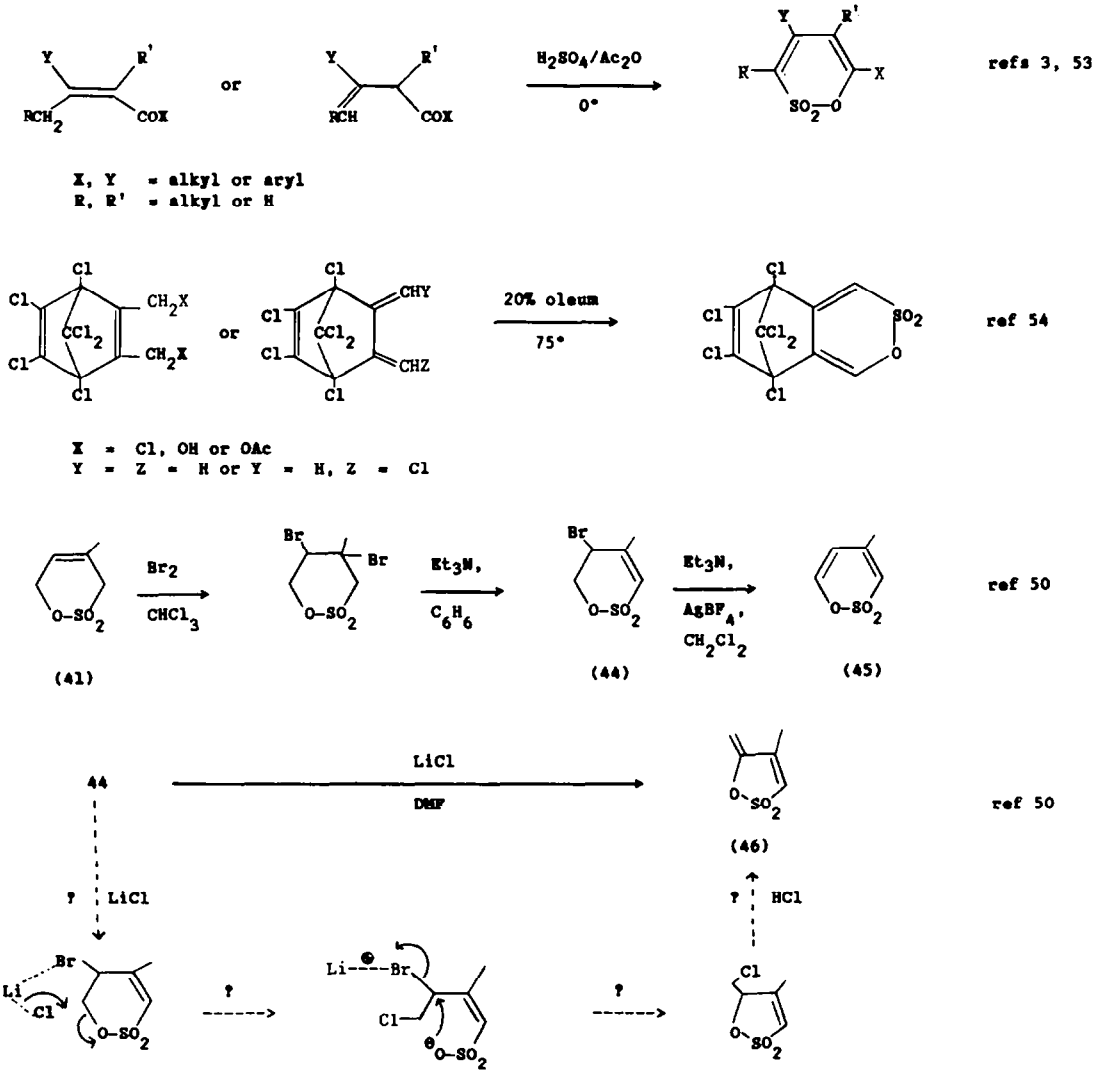
Table 4. β,γ-Unsaturated sultones from sulphonation of conjugated dienes

Diene	Sultone		Yield of sultone from sulphonation with: SO_3/dioxan in CH_2Cl_2, −25° to 0° (Ref. 51)	Yield of sultone from sulphonation with: SO_3/DMF in DMF, room temp. (Ref. 50)
1,3-Butadiene		(39)	3.5%	None
1,3-Pentadiene		(40)	15%	None
Isoprene		(41)	65%	48%
2,3-Dimethyl butadiene		(42)	ca. 80%	18%

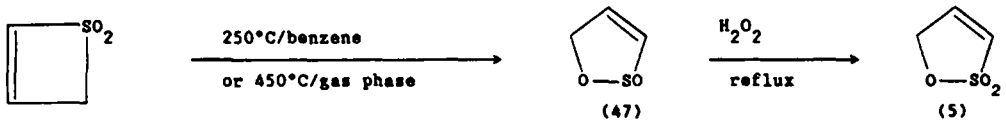


Scheme 10. Formation of 2-methyl-3-dimethylamino-2-butene-1,4-sultone.[52]

dehydrobromination route from 2-methyl-2-butene-1,4-sultone (**41**) to 2-methyl-1,3-butadiene-1,4-sultone (**45**), undergoes a ring contraction reaction on treatment with lithium chloride in refluxing DMF, giving 2-methyl-1,3-butadiene-1,3-sultone (**46**).[50] This reaction, with a possible mechanism, is also shown in Scheme 11.



Scheme 11. Syntheses of α,γ-di-unsaturated δ-sultones.



Scheme 12. 1-Propene-1,3-sultone via thermolysis of thiete-1,1-dioxide.[56]

2.2.2. *γ-Sultones.* 1-Propene-1,3-sultone (**5**) has been prepared by oxidation of the sultine (**47**) thermolysis product of thiete-1,1-dioxide[56] (Scheme 12).

Sultone **5** has also been made by distillation of 3-hydroxy-1-propene-1-sulphonic acid, which was obtained from propargyl alcohol via free radical sulphitation.[57]

1-Alkene-1,3-sultones (**48**) have been prepared by Connor *et al.*,[58] by dehydrobromination of 2-bromoalkane-1,3-sultones (**49**) prepared according to a method described by Püschel and Kaiser[59] (Scheme 13).

In a simplified modification described by Roberts *et al.*,[60] sodium 2-alkene sulphonate is made in 30–51% yield by sulphonation of a 1-alkene with a sulphur trioxide/dioxan 2 : 1 complex, followed by neutralisation. The crude sodium 2-alkene sulphonate, without separation from accompanying by-products, is treated with bromine to give **49** which is readily isolated and converted to **48** by treatment with excess triethylamine at room temperature.

Another route to unsaturated γ-sultones is by oxidation, using potassium peroxy sulphate, of the corresponding sultines (**50** and **51**), which can be made by the action of sulphur dioxide on vinylic Grignard reagents or aluminium compounds derived from propargyllic alcohols[61] (Scheme 14).

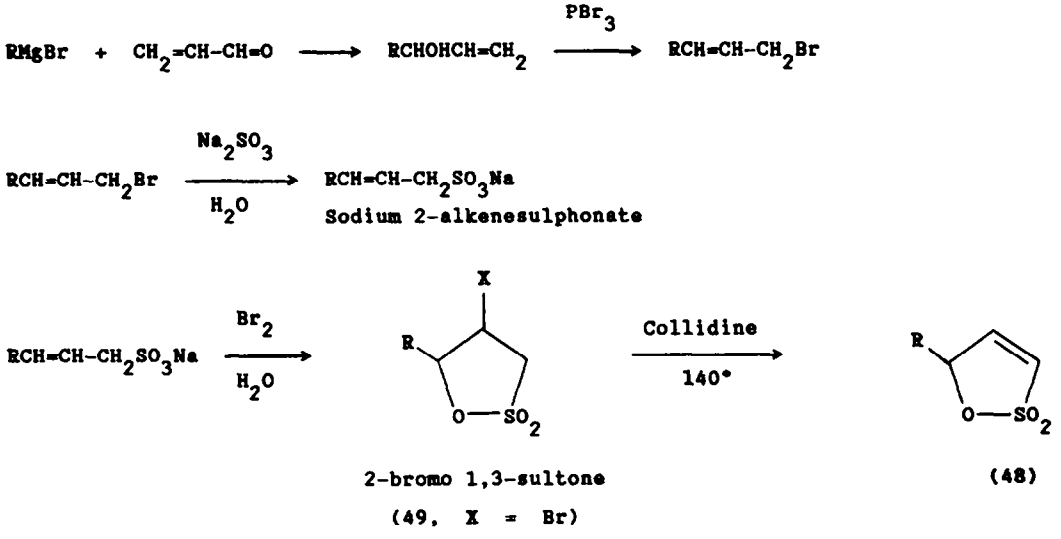
2.3. *β-Keto-γ-sultones and further sultones derived from them*

Stachel *et al.*[62] describe a general route to β-keto-γ-sultones, in which the ethyl ester of an α-hydroxy carboxylic acid is condensed with a sulphonyl chloride, followed by cyclisation in the presence of base (Scheme 15). The corresponding β-keto-γ-sultams can be prepared in the same way, starting from ethyl esters of amino acids.

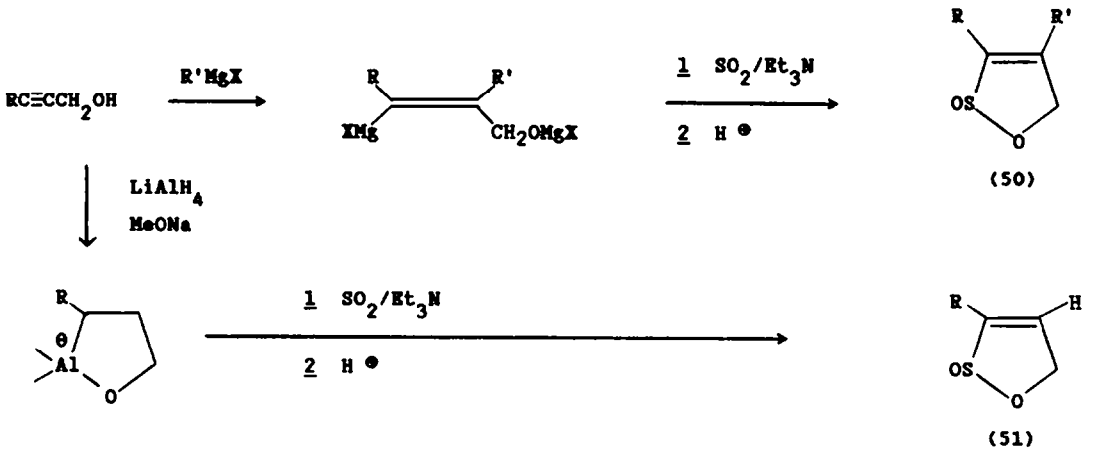
Further sultones can be made by reactions at the carbonyl group or at the α-carbon atom: a selection of the many examples given by Stachel *et al.*[62] is given in Scheme 16.

2.4. *Preparation of aromatic sultones*

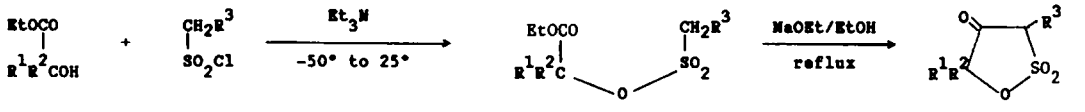
Aromatic sultones of general structures **54** and **55** can be prepared using similar methods. The most common procedure involves an elimination reaction of the corresponding hydroxy sulphonic



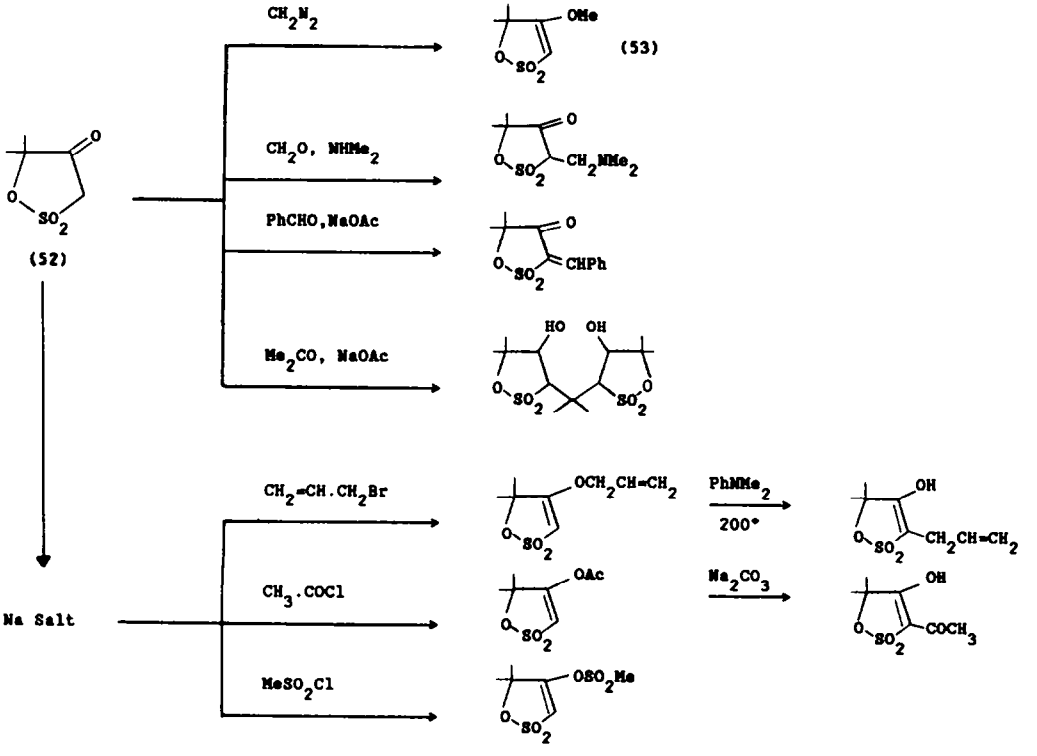
Scheme 13. Synthesis of 1-alkene-1,3-sultones.[58,59]



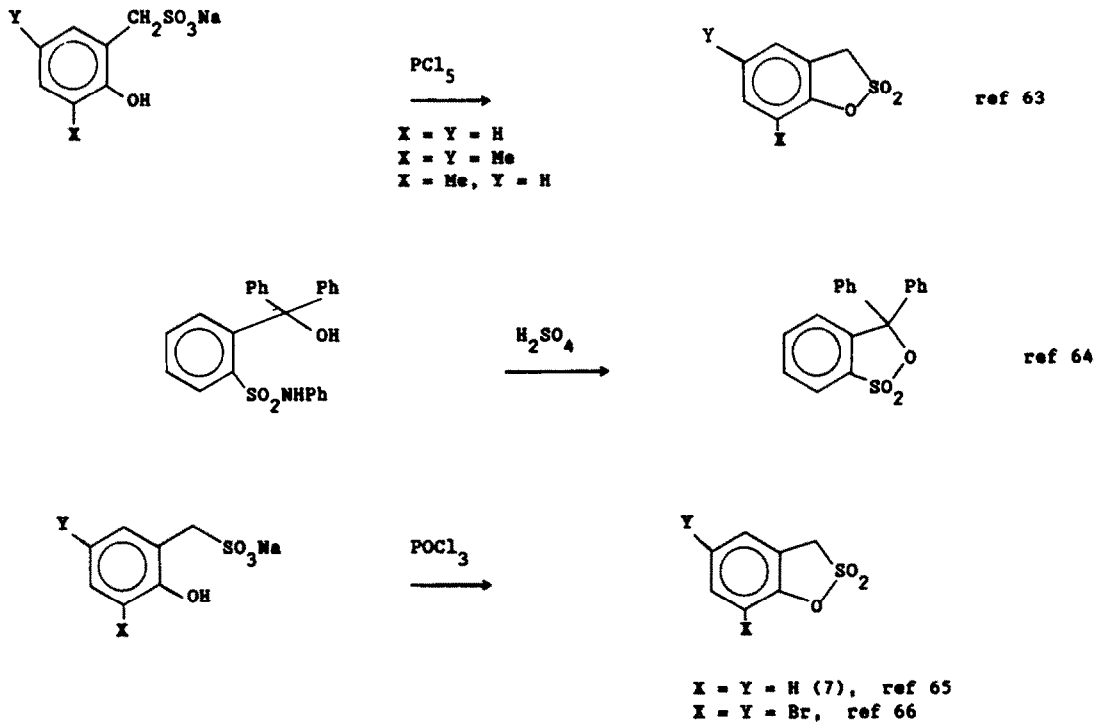
Scheme 14. Synthesis of unsaturated γ-sultines.[61]



Scheme 15. Synthetic route to β-keto-γ-sultones.[62]

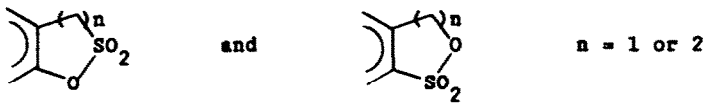


Scheme 16. Formation of further sultones from reactions of 3-methyl-2-oxo-butane-1,3-sultone.[62]



Scheme 17. Synthesis of aromatic sultones from hydroxy sulphonic acid derivatives.

acid derivative, using concentrated sulphuric acid, phosphorus pentachloride or phosphorus oxychloride.



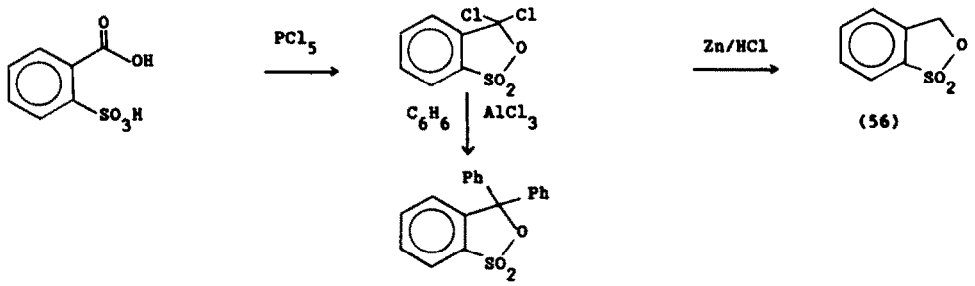
(54) (55)

Examples of these methods are shown in Scheme 17.

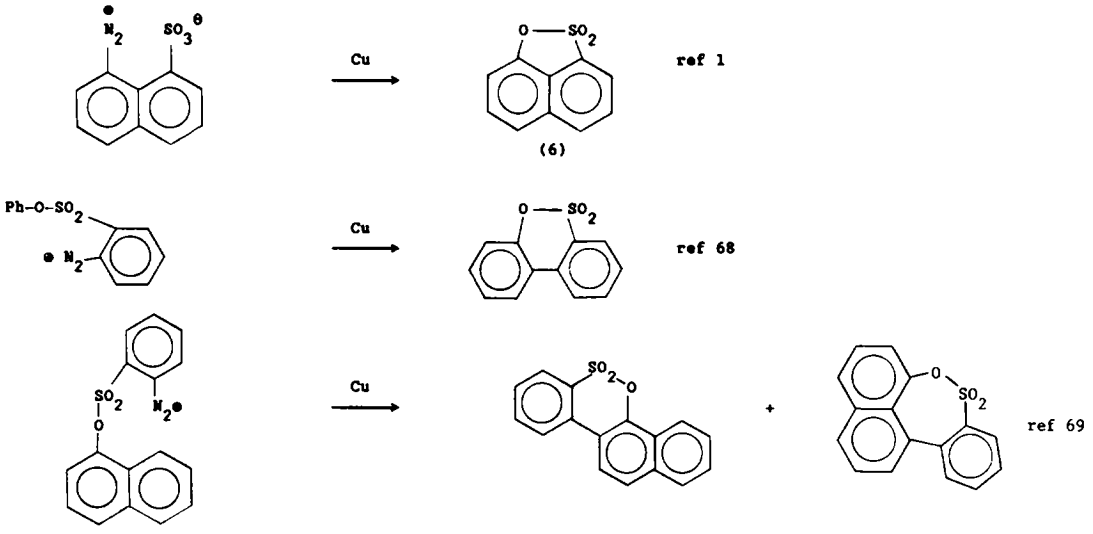
Other syntheses of 5-membered ring sultones[67] are shown in Scheme 18.

1,8-Naphthosultone (6) has been synthesised by treatment of a diazotised solution of 1-aminonaphthalene 8-sulphonic acid with powdered copper,[1] and polycyclic 6 and 7-membered ring sultones have been prepared from diazotised sulphonate esters, although some reactions lead only to mixtures of products (Scheme 19).

Drozd and Saks,[70] have reported the preparation of aromatic 6-membered ring sultones (54, $n = 2$) by the action of phenyl vinylsulphonate on various phenols, e.g. Scheme 20.



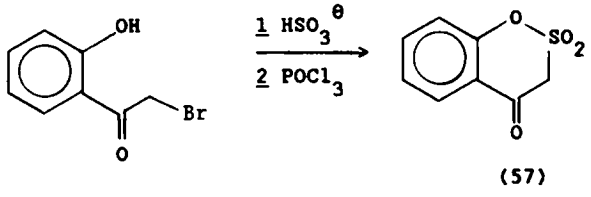
Scheme 18. Synthesis of aromatic γ-sultones from 2-sulphobenzoic acid.[67]



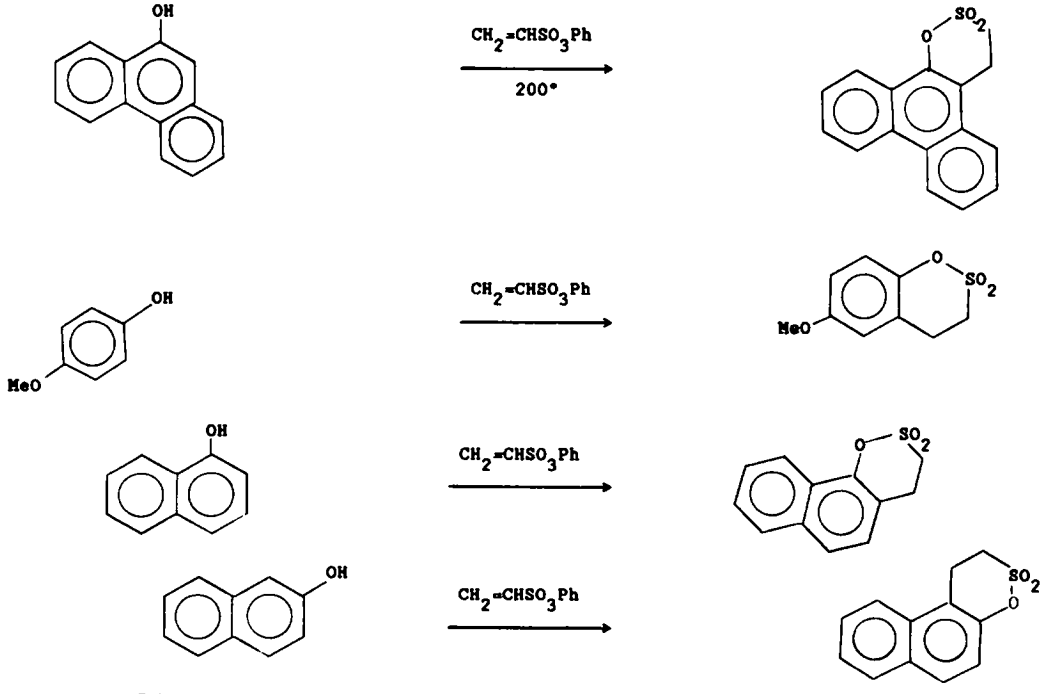
Scheme 19. Polycyclic aromatic sultones from diazotised amino sulphonic acids and their esters.

Sultones analogous to type **54** ($n = 2$) with functionality in the sultone ring have been synthesised via intramolecular condensation reactions of alkanesulphonylsalicylaldehydes,[71,72] as illustrated in Scheme 21.

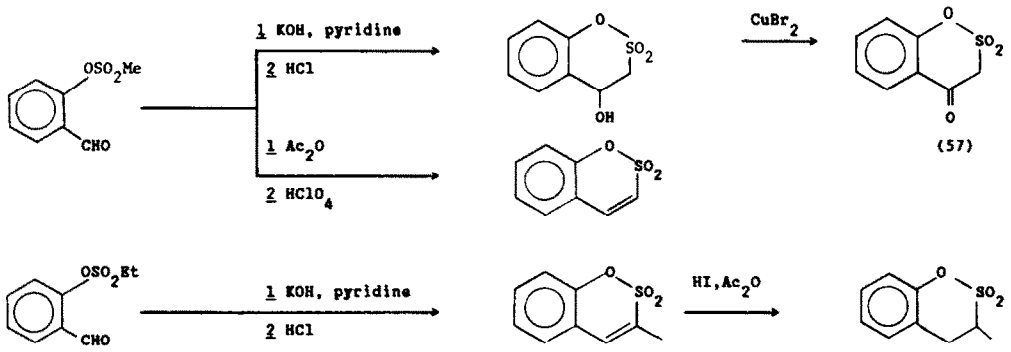
Sultone (**57**) has also been prepared by sulphitation of ortho hydroxy-α-bromoacetophenone and cyclisation using phosphorus oxychloride[73] (Eq. 5):



(5)

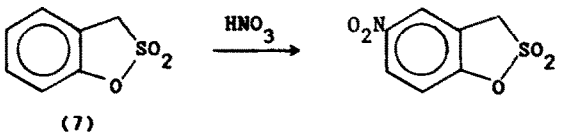


Scheme 20. Synthesis of aromatic δ-sultones by reactions of phenyl vinyl sulphonate.[70]

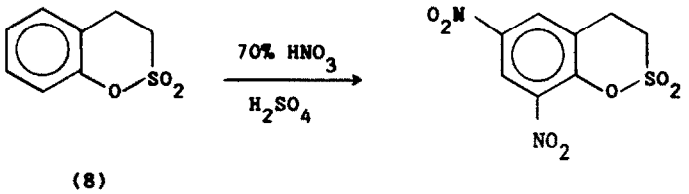


Scheme 21. Aromatic sultones from alkanesulphonylsalicylaldehydes.[71,72]

Aromatic sultones with groups in the aromatic rings can be made by electrophilic substitution reactions of the unsubstituted sultones, e.g. Eqs 6 and 7.



ref 74 (6)

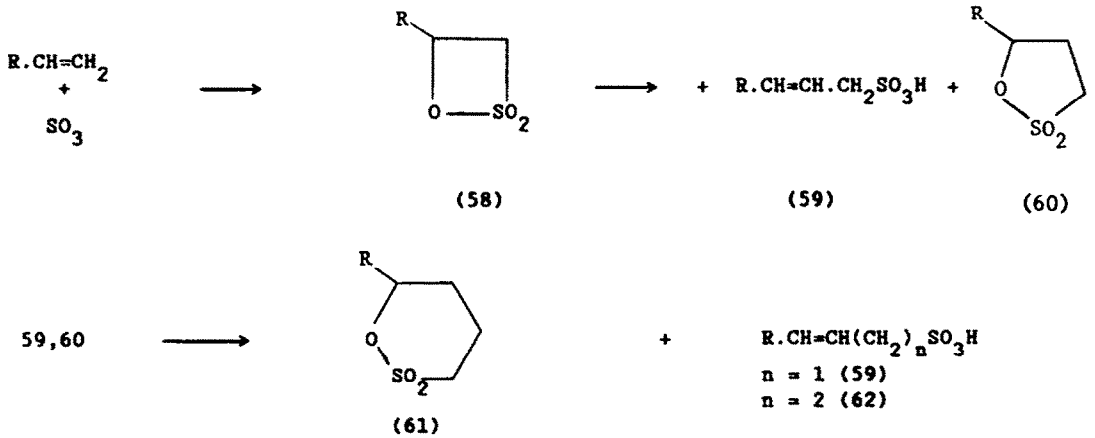


ref 75 (7)

3. REACTIONS OF SULTONES

3.1. *Saturated aliphatic sultones*

3.1.1. *Relative stabilities.* It has been shown[7,76] that the thermodynamic stability of the sultones decreases in the order $\delta > \gamma > \beta$, unlike the case for the lactones where the order is $\gamma > \delta > \beta$. The relative stability of the sultones is demonstrated in the sulphonation of unbranched 1-alkenes with free sulphur trioxide in the absence of a solvent (Scheme 22). The β-sultone (**58**) formed in the early

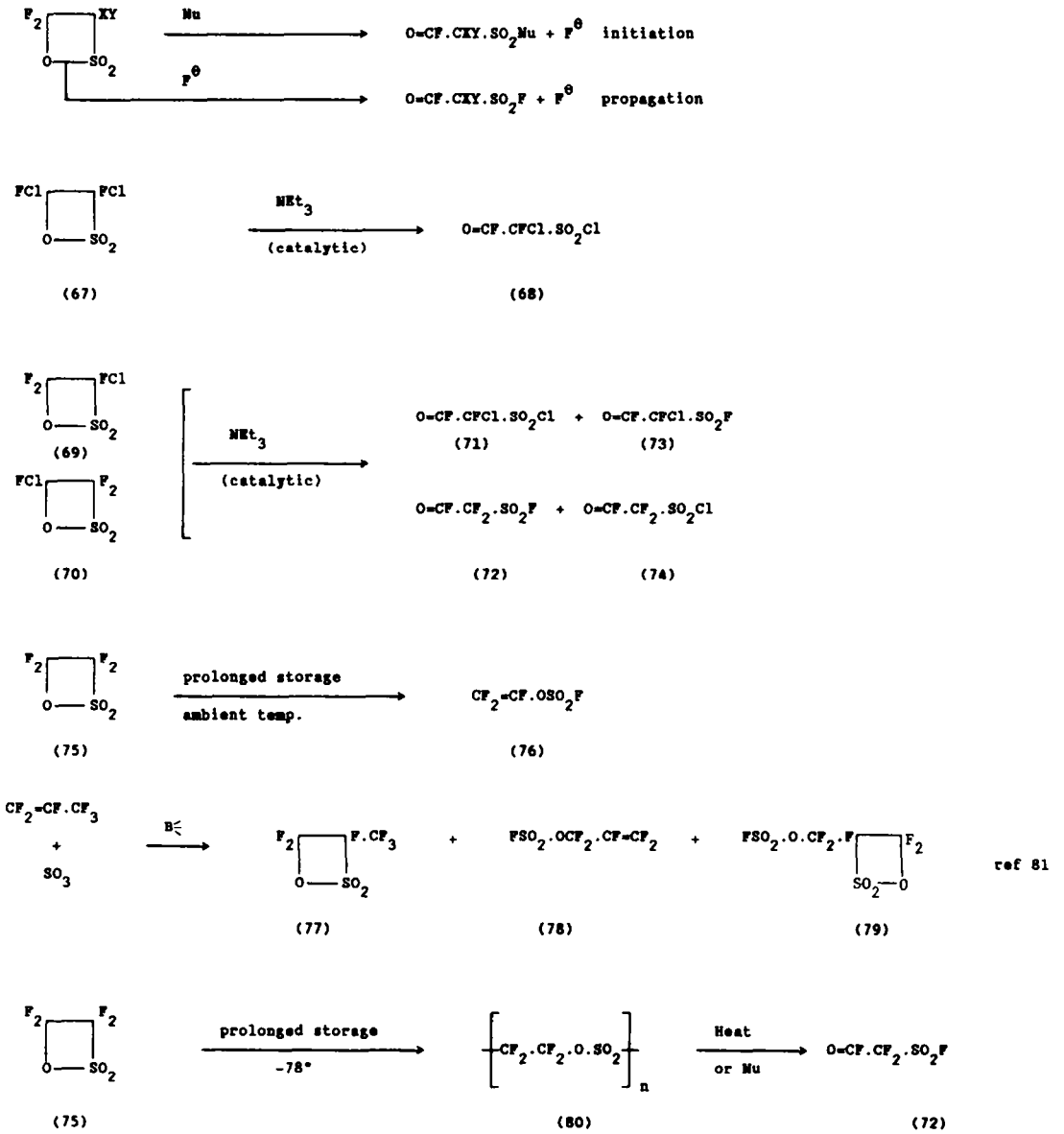


Scheme 22. Sulphonation of unbranched 1-alkenes.[77] R denotes a linear alkyl chain of variable length, such that the carbon number is the same for all organic compounds shown.

stages of the reaction breaks down thermally over a period of 1–2 minutes to give mainly 2-alkene sulphonic acids (**59**) and a mixture of γ (**60**) and δ (**61**) sultones.[77]

Further ageing of the sulphonation reaction mixture results in an increase in total sultone level and a change in the sultone composition from predominantly γ to predominantly δ.[78] These sultone isomerisation reactions could proceed via the 2- and 3-alkene sulphonic acids (**59** and **62**) respectively, via hydride transfer rearrangements of the corresponding β- and γ-zwitterions, or by a combination of both. Formation of δ-sultones by isomerisation of alkene sulphonic acids is a known reaction,[79] as is the isomerisation of γ- into δ-sultones at 10–20° in the presence of concentrated sulphuric acid.[80]

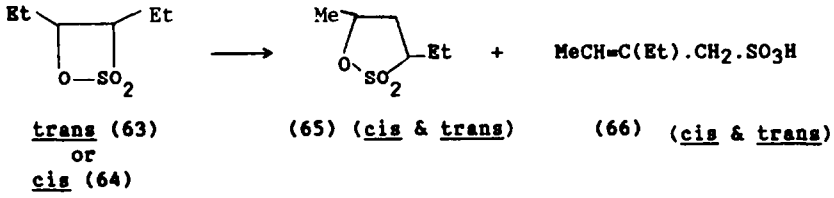
As mentioned in Section 2.1.6, β-sultones are formed stereospecifically in sulphonation of internal olefins.[43,47,48] The *trans*-β-sultones resulting from sulphonation of *trans* internal olefins are significantly more stable than their *cis*-isomers and α-olefin-derived β-sultones. Thus sulphonation of the two 3-hexenes separately with acetyl sulphate in dichloromethane gave solutions of the corresponding β-sultones. The *trans*-β-sultone (**63**) solution was essentially unchanged after 4 days



Scheme 23. Thermal decomposition reactions of fluorinated β-sultones. Taken from Ref. 35 except where otherwise indicated.

at ambient temperature whereas the *cis*-β-sultone (**64**) had completely decomposed after three days storage in solution at ambient temperature.[43]

The same β-sultones were formed by low temperature sulphonation of *cis* and *trans* 3-hexenes with sulphur trioxide in dichloromethane at −75°. They both decomposed, in refluxing chloroform, to mixtures of hexane-3,5-sultones (**65**) and 3-hexene-2-sulphonic acids (**66**), as shown in Eq. 8.[43]



Thermal decomposition reactions of fluorinated β-sultones are summarised in Scheme 23. The usual mode of decomposition involves heterolysis of the carbon-oxygen bond with elimination of halide ion from the β-position, giving rise to α-fluorosulphonylacyl halides.[35] This decomposition is initiated by nucleophiles (e.g. amines, dioxan, moisture) and is assumed to proceed via a chain process. Chloride ion is eliminated preferentially to fluoride ion; thus 1,2-dichloro-1,2-difluoroethane sultone (**67**) gives α-chlorosulphonyl chlorofluoroacetyl fluoride (**68**), and a mixture of the two isomeric chlorotrifluoroethane sultones (**69** and **70**) gives disproportionation products (**71** and **72**) along with isomerisation products (**73** and **74**).[34] An alternative type of decomposition,[35] involving heterolysis of the carbon-sulphur bond, is observed on prolonged storage of tetrafluoroethane sultone (**75**) in the absence of water, the product being trifluorovinyl fluorosulphate (**76**). Presumably hexafluoropropane-2,1-sultone (**77**) undergoes a similar decomposition, since sulphonation of hexafluoropropene in the presence of trivalent boron compounds gives, together with **77**, pentafluoroallyl fluorosulphate (**78**) and the β-sultone (**79**) derived from it.[81] In the absence of a trivalent boron compound, **77** is the major product. A third type of decomposition occurs when crystalline **75** is kept for a long time at −78°, the product being a polymer (**80**) which on heating or in the presence of nucleophiles gives fluorosulphonyl difluoroacetyl fluoride (**72**).[35]

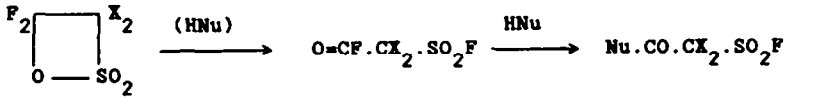
3.1.2. *Reactions of β-sultones.* Sulphur trioxide converts β-sultones into 1,3-dioxa-2,4-dithiacyclohexane-2,2,4,4-tetraoxides, usually referred to in the literature as carbyl sulphates or cyclic sulphonate-sulphate anhydrides. They may also be considered as cyclic esters of β-hydroxy alkane pyrosulphonic acids, and on this basis we have proposed the name pyrosultones.[82]

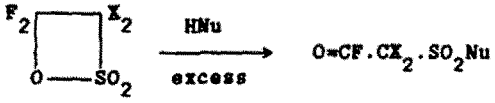
Formation of pyrosultones is often encountered as a side-reaction in olefin sulphonation. In some cases (e.g. sulphonation of ethylene[83]) high yields of pyrosultone (**81**) are obtained even when the olefin is in excess, and the (presumed) intermediate β-sultone cannot be detected. In other cases (e.g. sulphonation of 1-hexene with sulphur trioxide/dioxan) the formation of the pyrosultone (e.g. **82** R = n-C_4H_9) is slow, but can be catalysed by excess dioxan.[21]

Pyrosultones tend to have much greater thermal stability than β-sultones. For example, ethane pyrosultone **81** survives prolonged heating at 100° during its preparation from ethylene and sulphur trioxide.[83] Pyrosultones derived from fluoro-olefins decompose by a pathway analogous to the major breakdown reaction of fluoro-β-sultones, forming α-fluorosulphonyloxysulphonyl acyl fluorides.[35] Tetrafluoroethane pyrosultone (**83**) also decomposes by cleavage of the carbon sulphur bond, when treated with a catalytic amount of potassium fluoride at low temperature.[35]

Scheme 24 shows some examples of formation of pyrosultones and of their decomposition reactions.

β-Sultones react readily with nucleophiles, in some cases even with very weak ones such as acetic acid and methanol, giving β-substituted sulphonic acids or their salts. Some examples are shown in Table 5. In the case of fluorinated β-sultones, the reaction products tend to result from reaction of the nucleophile with the acyl halide grouping of the rearrangement product, although by using a large excess of the nucleophile substitution can be made to occur at sulphur (Eqs 9 and 10).[35]

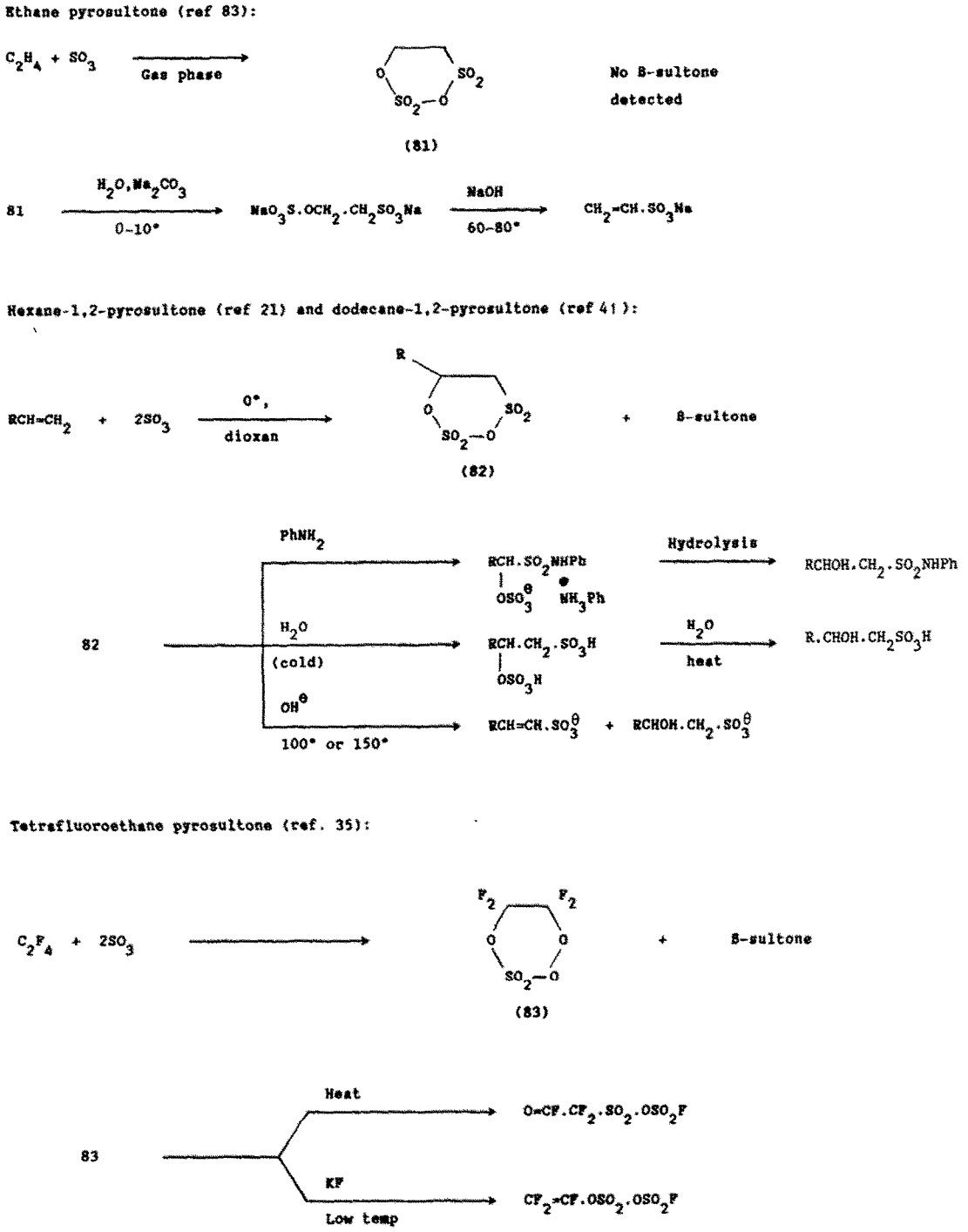




(10)

England *et al.*[34] describe the reactions of several fluorinated β-sultones with a large variety of nucleophiles.

3.1.3. *Hydrolysis of γ and δ-sultones.* Early studies on the hydrolysis rates of a number of primary, secondary and tertiary γ-sultones (i.e. propane-1,3-sultone derivatives bearing no, one or



Scheme 24. Formation and reactions of pyrosultones.

Table 5. Reactions of β-sultones with nucleophiles

β-Sultone	Nucleophile	Product	Reference
Derived from sulphonation of:			
n-$C_{10}H_{21}CH{=}CH_2$	H_2O	$C_{10}H_{21}\cdot CHOH\cdot CH_2SO_3H$	41
	$PhNH_2$, then NaOH	$C_{10}H_{21}\cdot CHNHPh\cdot CH_2SO_3Na$	41
n-$C_4H_9CH{=}CH_2$	Pyridine (Py)	$C_4H_9\cdot C\overset{\oplus}{H}Py\cdot CH_2SO_3^{\ominus}$	20
	MeOH then CH_2N_2	$C_4H_9\cdot CHOMe\cdot CH_2SO_3Me$	44
cis-EtCH=CHEt	HOAc, 3 days, ambient temp or $MeNH_2$/HOAc	*threo*-Et·CHOAc·CHEt·SO_3H	43
trans-EtCH=CHEt	$MeNH_2$/HOAc No significant reaction with HOAc alone at room temp.	*erythro*-Et·CHOAc·CHEt·SO_3H	43
cis-EtCH=CHEt	$MeNH_2$	*threo*-Et·$C\overset{\oplus}{H}NH_2Me$·CHEt·$SO_3^{\ominus}$	43
trans-EtCH=CHEt	$MeNH_2$	*erythro*-Et·$C\overset{\oplus}{H}NH_2Me$·CHEt·$SO_3^{\ominus}$	43
Cyclopentene[a]	H_2O	*trans*-2-Hydroxy-cyclopentane sulphonic acid[a]	22
cis-MeCH=CHMe	$PhNH_2$	*threo*-Me·CHNHPh·CHMe·SO_3Na	48
trans-MeCH=CHMe	$PhNH_2$	*erythro*-Me·CHNHPh·CHMe·SO_3Na	48

[a] Identification of the product was taken by Bordwell and Peterson[22] as evidence for the presence of the β-sultone in the reaction mixture from sulphonation of cyclopentene at 0° with a sulphur trioxide-dioxan complex. Thaler and du Breuil[43] have subsequently shown, by ^{13}C NMR, that the β-sultone is the major product from sulphonation of cyclopentene at low temperature.

two substituents in the γ-position) in water and in aqueous 2.8% dioxan were carried out by Nilsson[7] and by Bordwell *et al.*[26] They found these sultones to be hydrolysed predominantly by a unimolecular mechanism. This was later substantiated by Mori *et al.*[84,85] for hydrolysis of both γ and δ primary and secondary sultones at pH values below 9. Mori *et al.* demonstrated a bimolecular contribution to the overall hydrolysis rate at pH values above 9. Using ^{18}O-enriched water at pH > 12 they observed that 86% C—O fission and 14% S—O fission occurred, corresponding to the unimolecular and bimolecular mechanisms respectively.

Bordwell *et al.*[26] studied the effects of methyl substituents on hydrolysis rates of γ-sultones, and their relative rate and activation data are summarised in Table 6. They found that by comparison

Table 6. Relative rates and activation parameters at 40°C for hydrolysis of 5-membered ring sultones[26]

Substituents						Relative rate at 40°C	Sultone type	E_{act} (kcal mol^{-1})	$\Delta S\#$ (cal deg^{-1} mol^{-1})
At α-C		At β-C		At γ-C					
H	H	H	H	H	H	1.0	1°	20.4	−13.8
H	H	Me	H	H	H	0.21	1°	—	—
H	H	Me	Me	H	H	0.0035	1°	22.4	−18.7
Me	H	H	H	H	H	1.4	1°	19.4	−16.5
H	H	H	H	Me	H	1.3	2°	21.2	−10.5
Me	Me	H	H	Me	H	0.7	2°	18.4	−20.6
H	H	H	H	Me	Me	3100	3°	20.4	+2.3
H	H	Me	H	Me	Me	170	3°	19.2	−7.3
H	H	Me	Me	Me	Me	1.8	3°	20.3	−8.5
Me	H[a]	Me	H[a]	Me	Me	3.7	3°	19.6	−13.8
H	H	Ph	Me	Me	Me	6.3	3°	20.5	−9.8

[a] Depicted in Ref. 26 as the *trans*-isomer.

Table 7. Kinetic constants for hydrolysis in aqueous acetone (65 vol%) at 25°C and ionic strength 0.5[86]

Compound	$10 \times k$ (s^{-1})	E_{act} (kcal mol^{-1})	$\Delta S\#$ (cal deg^{-1} mol^{-1})
Propane-γ-sultone (**29**)	18.8	20.2	−17.1
	215[a]	20.4[a]	−13.8[a]
Butane-δ-sultone (**2**)	0.316	20.5	−24.0
	5.76[a]	20.0[a]	−20.0[a]
$CH_3CH_2SO_2OCH_2CH_3$	1.88	21.3	−17.9
	42.3[a]	20.9[a]	−13.2[a]

[a] In water.

with 1°, 2° and 3° halides the increases in rate were less than expected by a factor of 10^3. This fact coupled with the observation that the hydrolysis rates appeared to be controlled not by ring strain, or activation energy, but by the activation entropy, $\Delta S\#$, led to the conclusion that heterolysis of the C—O bond, which must occur for the unimolecular process, is accompanied by a rotation around the C—C bonds of the sultone ring. If these carbon atoms are substituted with methyl groups then rotation is restricted, which results in the entropy of activation becoming increasingly negative, and consequently an overall rate retardation.

Nagayama *et al.*[86] showed that hydrolyses of propane-1,3-sultone (**29**), butane-1,4-sultone (**2**) and ethyl ethanesulphonate have very similar activation energies, indicating that there is very little ring strain in the sultones, but the hydrolysis rates are in the ratio 37 : 1 : 7. These findings were again rationalised in terms of entropy of activation differences as shown in Table 7.

Sultone hydrolysis can give alkenesulphonates by elimination, or hydroxyalkanesulphonates by substitution. As shown in Table 8, the ratio of elimination to substitution products increases with increasing substitution at the γ-position of γ-sultones or at the δ-position of δ-sultones; there are also indications that it increases with increasing alkyl chain length in γ-alkyl γ-sultones.

Elimination from long chain 1,4-sultones is favoured from inside the ring, giving 3-alkene sulphonates, whereas Püschel and Kaiser found that the 33% yield of unsaturated products obtained from long chain 1,3-sultone hydrolysis is composed of 30% of the 3-alkenesulphonate and only 3% of the Δ^2 isomer.[59]

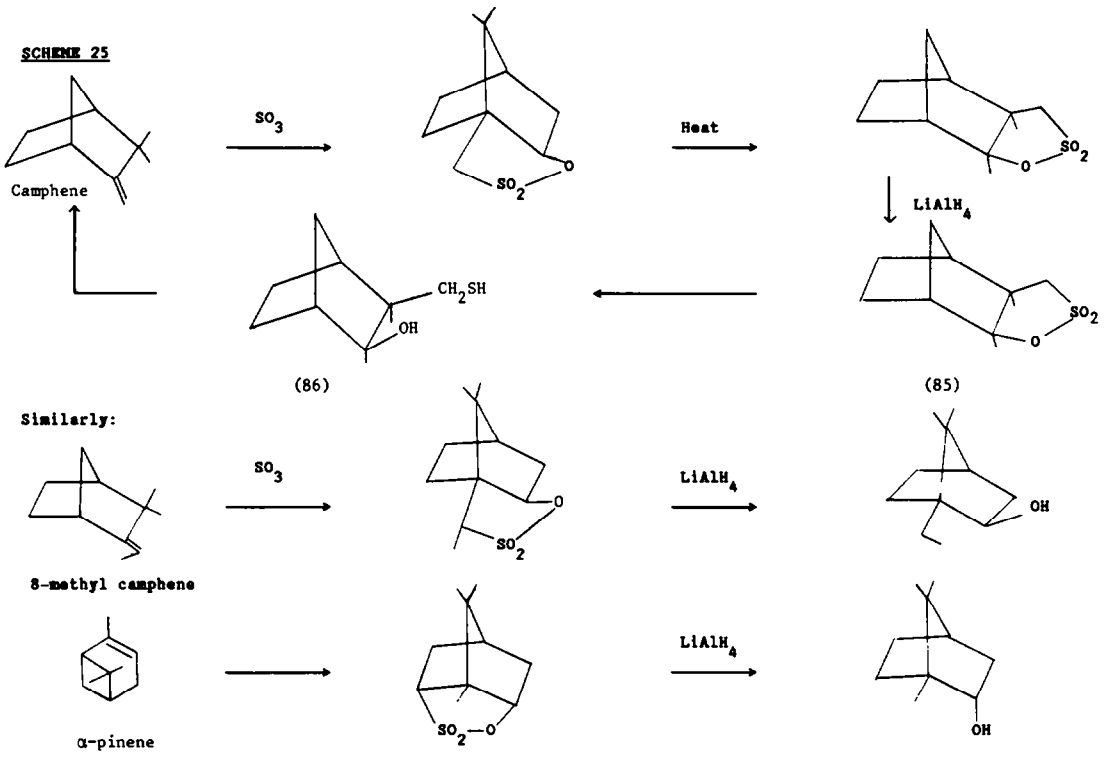
Nilsson's findings[7] on the relative rates of unimolecular hydrolysis of γ- and δ-sultones are in good agreement with those of Nagayama *et al.*,[86] his value for the ratio k(propane-1,3-sultone) : k(butane-1,4-sultone) being 50 : 1. Nilsson also found that the ε-sultone pentane-1,5-sultone (**84**) has a unimolecular hydrolysis rate about 5 times that of butane-1,4-sultone.

3.1.4. *Reaction of γ-sultones with lithium aluminium hydride.* Wolinsky *et al.*[87,88] prepared γ-sultones from several terpenes (camphene, α-pinene, α-ethylapopinene and 8-methylcamphene) and used the products from their reduction with lithium aluminium hydride to confirm their structures.

Initial reduction leads to formation of a cyclic sulphinate ester (sultine), e.g. **85**, which is further reduced to the mercapto alcohol, e.g. **86**, and finally to the fully sulphur-free products (Scheme 25).

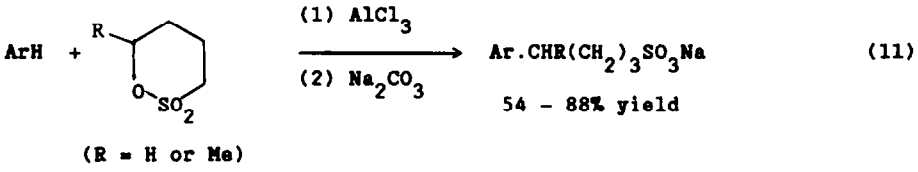
Table 8. Variation with sultone structure of % elimination on hydrolysis

Sultone	% Elimination on hydrolysis in water	Reference
Propane-1,3-sultone (29)	0	7
Butane-1,3-sultone (60, R = Me)	1	7
3-Methylbutane-1,3-sultone (13)	15	7
2,3-Dimethylbutane-1,3-sultone (12)	38	26
2,2,3-Trimethylbutane-1,3-sultone (17)	62	26
Hexane-1,3-sultone (60, R = n-C_3H_7)	22	59
Dodecane-1,3-sultone (60, R = n-C_9H_{19})	33	59
Butane-1,4-sultone (2)	0	7
Hexadecane-1,4-sultone (61, R = n-$C_{12}H_{25}$)	30	86



Scheme 25. Reactions of terpene-derived γ-sultones with lithium aluminium hydride.[87,88]

3.1.5. *Friedel–Crafts reactions with γ and δ-sultones.* Truce and Hoerger[65] showed that butane-1,4-sultone (**2**) and pentane-1,4-sultone (**61**, R=Me) react with several aromatic compounds in the presence of aluminium chloride to give the corresponding 4-aryl-1-sulphonates in a similar fashion to the Friedel–Crafts alkylation with lactones (Eq. 11).

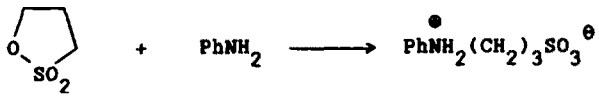


(11)

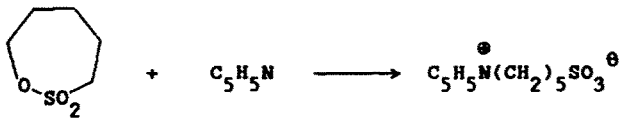
Similarly, propane-1,3-sultone (**29**) reacts with aromatic compounds to yield 3-arylpropane sulphonates.[89] Unlike Friedel-Crafts alkylations involving straight chain ethers, primary alkyl halides, primary alcohols, alkyl esters, alkyl sulphates and sulphonates, the reactions with sultones proceed without rearrangement of the carbon skeleton, as do the alkylations of benzene with γ-butyrolactone and δ-valerolactone. Reaction of dodecylbenzene with **29** resulted in only 20% alkylation due to the insolubility of the aluminium chloride/sultone complex in this reagent.

3.1.6. *Reactions of γ and δ sultones with nucleophiles.* Unlike γ- and δ-lactones, which behave as acylating agents (i.e. nucleophilic attack leads to acyl-oxygen fission), alkane γ- and δ-sultones behave as sulphoalkylating agents in their reactions with nucleophiles, i.e. alkyl-oxygen fission rather than sulphonyl-oxygen fission occurs.[90] These reactions have been reviewed by Fischer[91] and Hoerger.[92].

Willems[5] obtained high yields of anilinoalkane sulphonic acids by reaction of several γ-sultones with aniline, and of pyridino-sulphobetaines by reaction of a wide range of γ- and δ-sultones and also the ε-sultone **84**, with pyridine (e.g. Eqs 12 and 13).



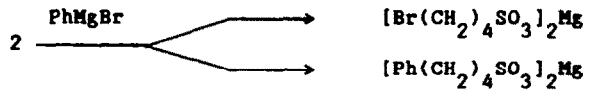
(29) (12)



(84) (13)

Helberger *et al.*[16,90,93] obtained substitution products by reaction of a wide range of nucleophiles with propane-1,3-sultone (**29**) butane-2,4-sultone (**87**) and butane-1,4-sultone (**2**). Yields of substitution products from reactions with the various nucleophiles are shown in Table 9, which also includes data reported by Furukawa *et al.*[89]

Grignard reagents and related organo-metallic compounds can also be sulphoalkylated by sultones. Willems[5] prepared magnesium hexanesulphonate in 60% yield from equi-molar amounts of ethyl magnesium bromide and butane-1,4-sultone (**2**). The reaction of phenyl magnesium bromide with **2** gave a mixture of magnesium 4-bromo-1-butane sulphonate and magnesium 4-phenyl-1-butane sulphonate, a finding which was interpreted in terms of nucleophilic attack by bromide competing with nucleophilic attack by the phenyl group[94] (Eq. 14).

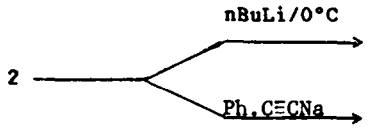


(14)

Sulphoalkylation has also been shown to occur readily with *n*-butyl lithium and with phenylethynylsodium[94] (Eqs 15 and 16).

Table 9. Yield of sulphoalkylation products from reactions of γ- and δ-sultones with nucleophiles. Data from references 16, 90 and 93, unless otherwise indicated

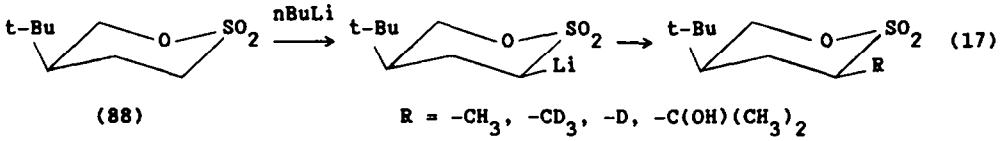
	Yield		
Sultone	$CH_2(CH_2)_nCHR \cdot SO_2 \cdot O$		
Reagent	$n = 1$,[29] R = H	$n = 1$,[87] R = CH_3	$n = 2$,[2] R = H
C_5H_5N	100	97	98
NH_3	87	90	85
$PhN(CH_3)_2$		94	
Quinoline		97	
KCN	77 (Ref. 89)	80	92
KCNS	95 (Ref. 89)	96	94
KI		70	100
KF		Reaction described, yield not given	—
K/NaBr		96	
NaSH		100	100
$R'C_6H_4OH/Na$	88 (Ref. 89) ($R' = C_9H_{19}$)	86 ($R' = H$)	90 ($R' = H$)
PhSNa		98	93
K Phthalimide		95	97
CH_3CO_2Na		100	100
$PhCO_2Na$		60	60
Sodium oleate, $C_{17}H_{33}CO_2Na$		65	65
R'CONHNa	100 (Ref. 89) ($R' = C_{11}H_{23}$)	80 ($R' = CH_3$)	80
$C_{12}H_{25}OH/NaOH$	87 (Ref. 89)	over 90	



$$n\text{-}C_8H_{17}SO_3Li \quad (15)$$

$$Ph.C{\equiv}C(CH_2)_4SO_3Na \quad (16)$$

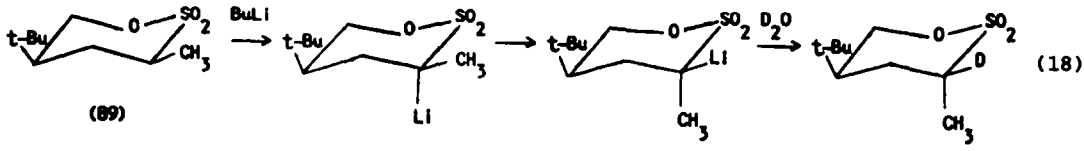
However, *n*-butyl lithium can also metallate sultones in the α-position. Thus when 3-*tert*-butylbutane-1,4-sultone (**88**) was treated with *n*-butyl lithium at −78°C in tetrahydrofuran, proton abstraction from the 1-position occurred.[95] Subsequent quenching of the lithio-derivative with methyl iodide, deuterium oxide or acetone gave the corresponding equatorially substituted 1,4-sultones (Eq. 17).



(88) (17)

R = $-CH_3$, $-CD_3$, $-D$, $-C(OH)(CH_3)_2$

The preference for equatorial lithiation was shown by treatment of *cis*-4-tert-butyl-pentane-2,5 sultone (**89**) with *n*-butyl lithium, quenching with D_2O after allowing the mixture to equilibrate. The resultant sultone has an α-deuterium atom in the equatorial position (Eq. 18).



(89) (18)

Other sulphoalkylations at carbon have been achieved in reactions of **2** with sodium derivatives of diethyl malonate and ethyl acetoacetate,[94] in 95% and 82% yields, respectively.

Primary or secondary perfluoroalkoxides, made *in situ* by treatment of perfluoroacyl fluorides or perfluoroketones respectively with alkali metal fluorides, are sulphopropylated by **29** in high yields[96] (Eqs 19 and 20).

$$(CF_3)_2CO + CsF \longrightarrow (CF_3)_2CF.OCs \xrightarrow{29} (CF_3)_2CF.O(CH_2)_3SO_3Cs \quad (19)$$

98% yield

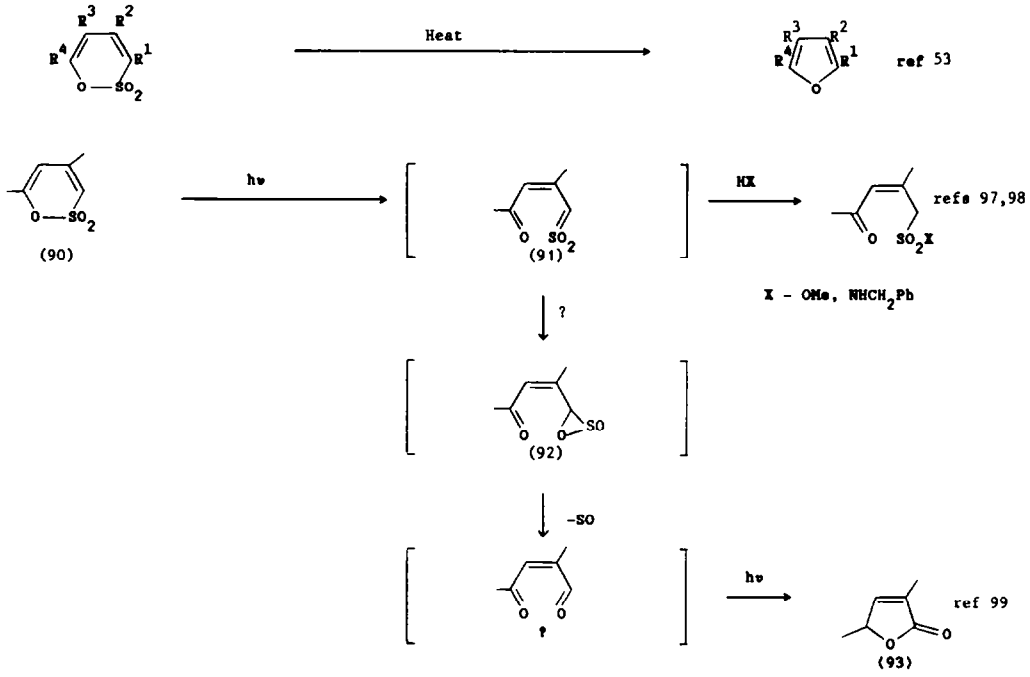
$$n\text{-}C_6F_{13}.CO.F + KF \longrightarrow nC_7F_{15}.OK \xrightarrow{29} n\text{-}C_7F_{15}.O(CH_2)_3SO_3K \quad (20)$$

72% yield

3.2. *Reactions of unsaturated sultones*

3.2.1. *Thermal and photochemical decomposition.* Morel and Verkade, who developed the route to α,γ-di-unsaturated δ-sultones based on sulphonation of unsaturated ketones[3,53] (Scheme 11, Section 2.2.1), showed that these sultones decompose on heating to form furans, thus providing a general synthetic method for substituted furans.[53] Photolysis of α,γ-di-unsaturated δ-sultones (e.g. **90**) in the presence of methanol or benzylamine was found by DeMayo *et al.* to give ketosulphonic acid derivatives, which can be envisaged as arising from nucleophilic attack on intermediate sulphenes (e.g. **91**).[97,98] In the absence of a nucleophile, photolysis of α,γ-di-unsaturated δ-sultones (e.g. **90**) with no substituents in the α-position gave unsaturated γ-lactones (e.g. **93**),[99] presumably via loss of sulphur monoxide from the α-sultine (e.g. **92**) forms of the sulphenes.[99,100] Examples of these thermal and photolytic reactions are shown in Scheme 26.

β-unsaturated δ-sultones made by sulphonation of conjugated dienes (Section 2.2.1) tend to decompose at temperatures above about 100°, in what appears to be a retro-Diels-Alder reaction.



Scheme 26. Thermal and photochemical reactions of α,γ-di-unsaturated δ-sultones.[77]

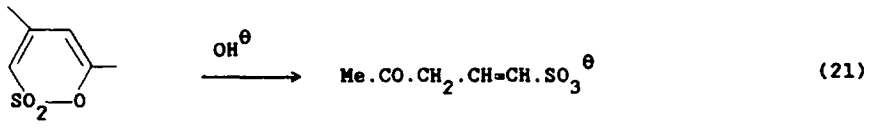
Scheme 27. Thermal decomposition of 2-methyl-2-butene-1,4-sultone.[51]

Thus 2-methyl-2-butene-1,4-sultone (**45**) gave the maleic anhydride-isoprene Diels–Alder adduct on heating with maleic anhydride at 105°[51] (Scheme 27).

3.2.2. *Reactions with nucleophiles and bases.* Moiseenkov and Zaks, with their co-workers, have reported studies on the reactions of several β-unsaturated δ-sultones with a wide range of nucleophiles and bases. β-unsaturated δ-sultones behave as sulphoalkenylating agents in their reactions with amine nucleophiles, the Z-stereo chemistry of the double bond being retained.[101] With hydride complexes they react predominantly as sulphoalkenylating agents toward hydride ion, with reaction at the sulphur atom (the major site of reduction in the case of saturated sultones; see Section 3.1.4) being a minor side reaction.[101] Reactions with water or methanol give products in which hydroxide or methoxide respectively have been sulphoalkenylated, in these cases with some double bond geometrical isomerisation.[101] Treatment with strong bases (e.g. methyl lithium, sodium amide, potassium tert-butoxide) gives stereospecific 1,4 elimination, forming 1,3-diene-1-sulphonates.[102] These substitution and elimination reactions are illustrated in Scheme 28.

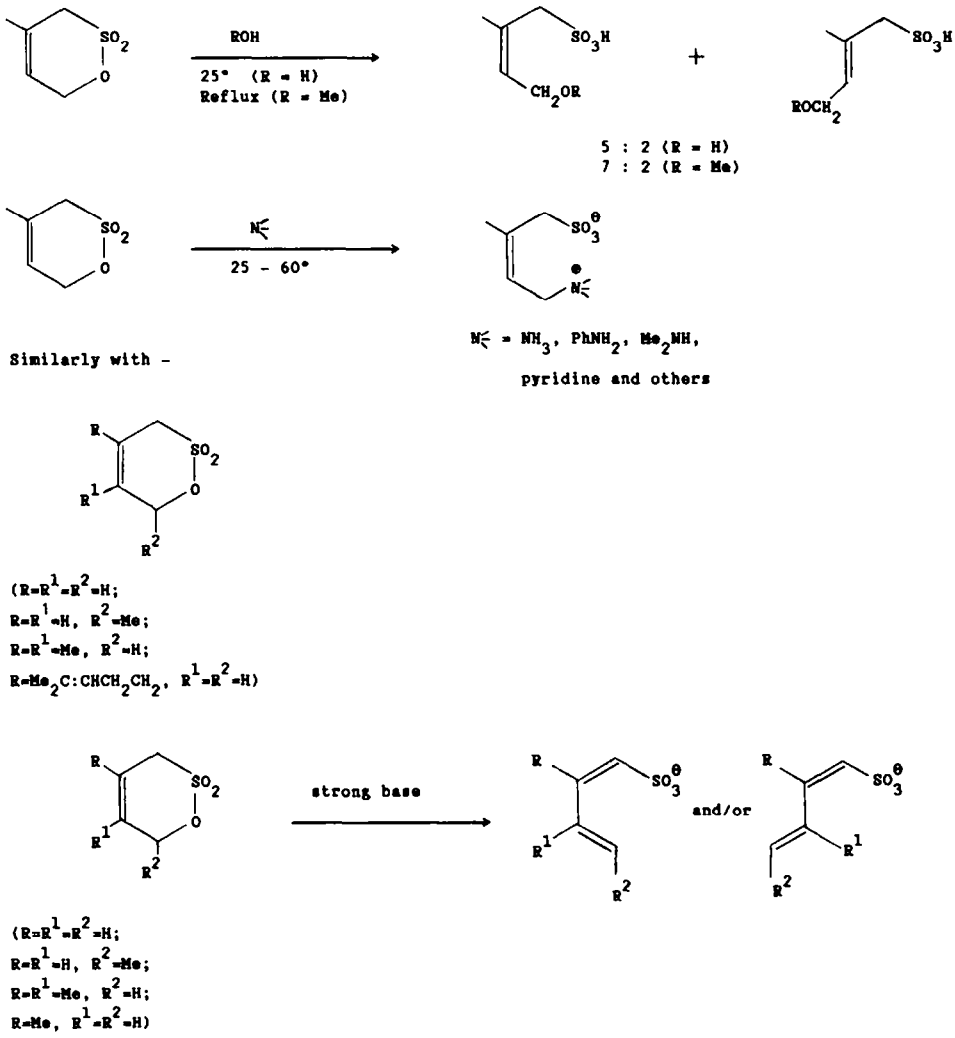
The double bond in β-unsaturated δ-sultones has a large effect in enhancing hydrolytic reactivity. The first order rate constant for hydrolysis of 2,3-dimethyl-2-butene-1,4-sultone, **42**, in 2.75% aqueous dioxan at 30° is reported[103] to be 0.08% min^{-1}, which is 223 times the rate constant for hydrolysis of butane δ-sultone, **2**, in water at 30°.[7]

In contrast the hydrolysis of the α,γ-diunsaturated sultone 2-methyl-1,3-pentadiene-1,4-sultone (**90**) in water is very slow at 30°, having a half-life of about 6 weeks.[103] The main product from basic hydrolysis of **90** is 2-methyl-1-pentene-4-one-1-sulphonate (Eq. 21), presumably resulting from attack at sulphur with displacement of the enolate followed by ketonisation.

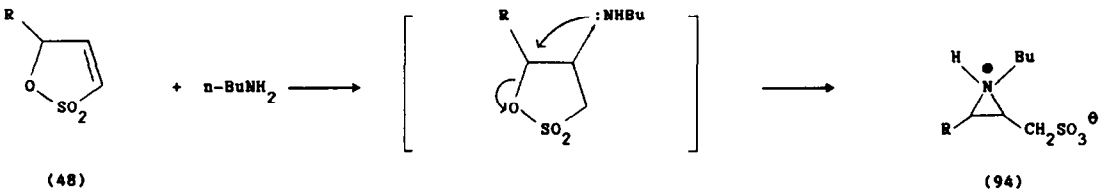


(90) (21)

There are few reports in the literature on reactions of unsaturated-γ-sultones. 1-Alkene-1,3-sultones (**48**) have been shown to react with butylamine *via* Michael addition to the double bond, but the final reaction product is an aziridinium betaine (**94**) derived from an intramolecular nucleophilic attack by the nitrogen lone pair of the Michael adduct[104] (Scheme 29).



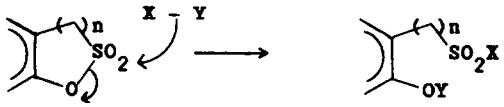
Scheme 28. Reactions of β-unsaturated δ-sultones with nucleophiles and bases.[101,102]



Scheme 29. Reaction of 1-alkene-1,3-sultones with butylamine.[104]

3.3. *Reactions of aromatic sultones*

Early studies were concerned with the comparison of the reactions of aliphatic and aromatic sultones with nucleophiles and were reviewed by Mustafa in 1954.[4] Unlike aliphatic sultones which usually undergo nucleophilic displacement at carbon (ring-opening by C—O bond fission) aromatic sultones of type **54** do not have this opportunity, since this would involve either nucleophilic attack at the benzene ring or aryl-oxygen bond fission, resulting in the formation of an aryl cation. Instead, nucleophilic displacement in these aromatic sultones takes place at sulphur, resulting in S—O bond fission (Eq. 22).



(54) (95) (22)

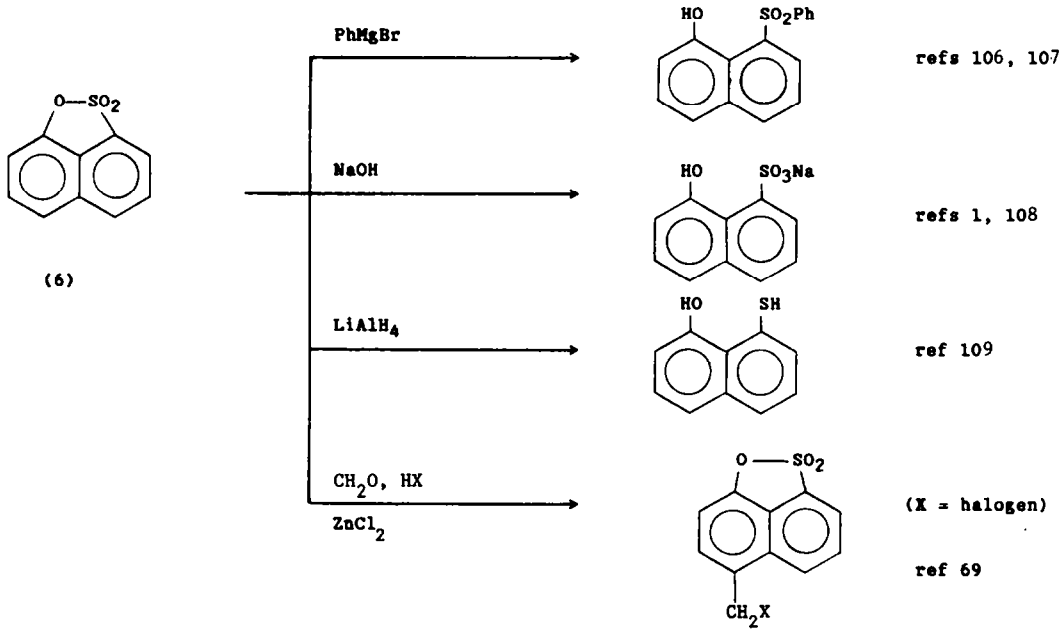
Thus **7** gives alkali salts of (2-hydroxyphenyl)methane sulphonic acid on heating with alkalis[105] and **8** gives **95** ($n = 2$, X = C_6H_5, Y = MgBr, aromatic unit = benzene ring) on treatment with phenyl magnesium bromide.[92,94]

1,8-Naphthosultones, e.g. **6**, which have been extensively studied by Mustafa *et al.*[4] undergo similar reactions with nucleophiles (Scheme 30).

Compound **6** condenses with paraformaldehyde and hydrogen halide in the presence of zinc chloride,[69] to give the 5-halomethyl sultone (Scheme 30) and can also be acylated, aroylated and arylsulphonated in the 5-position by a Friedel-Crafts reaction without disturbing the sultone ring.[110]

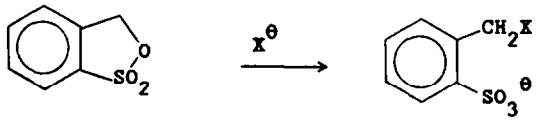
In contrast to sultones of type **54**, sultone **56** behaves similarly to aliphatic sultones in its reactions with nucleophiles[99] (Eq. 23).

More recent work has been concerned with the rates and mechanism of hydrolysis of sultones of type **54**, prompted by the observations that biologically active 5-membered ring cyclic phosphates



(6)

Scheme 30. Reactions of 1,8-naphthosultone.



(23)

(56)

(X = I, SH, $PhCH_2CO_2$, $C_nH_{2n+1}CO_2$, MeCONH)

and lactones exhibit very large rate enhancements with respect to their open chain analogues.[111-113] Similarly, the 5-membered ring sultone **7** was found to exhibit a rate enhancement of 6.8×10^5 compared to the open chain analogue, phenyl α-toluenesulphonate (**96**).[113]

The 6-membered ring sultone **8** also shows a hydrolysis rate enhancement over **97** although only by a factor of 57.[115] This trend is continued with the 7-membered ring sultone, **97** (Table 10) which is hydrolysed only three times as fast as **96**, but at a temperature 25° higher.[115] Rate constants for these reactions, and for hydrolyses of derivatives of **7** with substituents in the aromatic ring,[116] are given in Table 10.

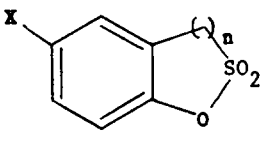
Similar rate enhancements have also been observed for cyclic 5-membered sulphates compared to their open chain analogues. For example, catechol sulphate (**98**) is hydrolysed 2×10^7 times faster than diphenyl sulphate (**99**).[117]

As yet whether the hydrolysis of 5-membered ring cyclic sulphonates proceeds via a stepwise or a concerted mechanism has not been unequivocally proved, although the bulk of the evidence is in favour of the concerted (S_N2) pathway.

A sulphene mechanism has been shown to occur for alkaline hydrolysis and aminolysis of open-chain aryl α-toluenesulphonates[118] (Scheme 31).

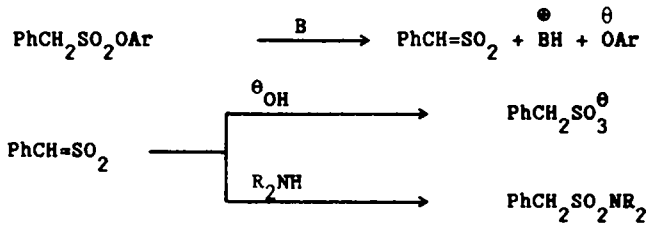
However, this mechanism does not apply to the hydrolysis[116] and aminolysis[118] of the sultones of type **54**: it has been argued that the sulphene mechanism is disfavoured for the sultones because the transition state for sulphene formation would have the "incipient sulphene" in its less stable

Table 10. Rate data for hydroxide ion catalysed hydrolysis of selected cyclic and open chain sulphonate esters[114-116]

Sultone  X =	n = 1		k_{OH^-}, 25°C ($l\ mol^{-1}\ sec^{-1}$)
$-NO_2$	1		1.4×10^{-3}
-Br	1		95.1
-H	1	(7)	37.4
$-CH_3$	1		24.0
$-OCH_3$	1		13.6
-H	2	(8)	2.8×10^{-3}
H	3	(97)	1.6×10^4 (50°C)
$Ph.CH_2.SO_2OPh$ (96) †			4.9×10^{-5}

Hydrolysis conditions—1.50 to 11.5×10^{-4} M substrate; 0.5 M $NaClO_4$ ($\mu = 0.5$); measurements done at constant pH maintained by addition of 0.2 M NaOH using autotitrator. Thermostatted at 25°C.

† Extrapolated to 0% dimethoxyethane (DME) from measurements in solutions containing DME.[114]

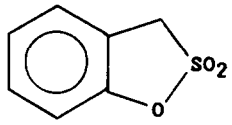
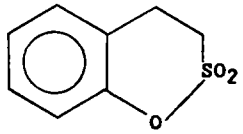
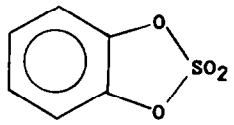
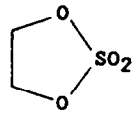
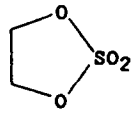


Scheme 31. Sulphene mechanism for alkaline hydrolysis and aminolysis of aryl α-toluenesulphonates.

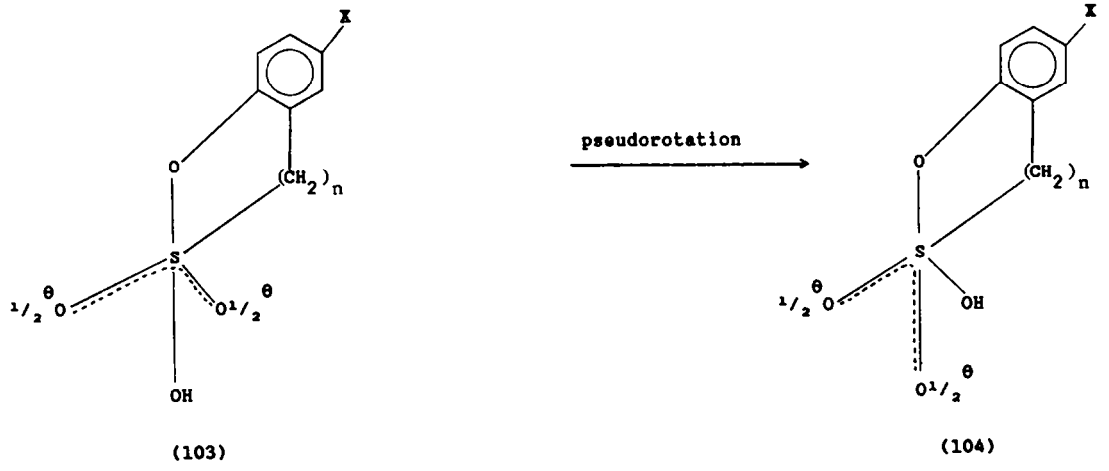
form with the oxygen atoms in a plane perpendicular to that of the substituents on the carbon atom bonded to sulphur.[119]

A pathway involving nucleophilic attack at sulphur has several factors in its favour, not least of which is the very small O—S—C bond angle in the 5-membered ring sultones **54** (n = 1). Table 11.

Table 11. Bond angles at sulphur of some cyclic sulphate and sulphonate esters. Except where otherwise indicated, data are from Kaiser and Kézdy[120]

Ester		OSC or OSO bond angle	Hydrolysis rate constant, k_{OH^-}, 25° (l mol^{-1} sec^{-1})
	(7)	96.1	37.4
	(8)	101.4*	2.8×10^{-3}
	(98)	97.1*	18.8
$(PhO)_2SO_2$	(99)	109*	8.9×10^{-3}
	(100)	93.6* (ref 121)	8.33 (ref 118)
	(101)	98.4* (ref 121)	About 20 times as fast as dimethyl sulphate** (ref 121)
$(MeO)_2SO_2$	(102)	109	2.14×10^{-3} at 9.97** (ref 122)

* Hydrolysis proceeds mainly (ca 86%) by C—O cleavage.
** Hydrolysis proceeds by C—O cleavage.



(103) (104)

n = 1, 2 or 3. X as in Table 10

Scheme 32. Possible pentacoordinate intermediates in hydrolysis of aromatic sultones.[120]

shows the very small bond angles for 5-membered ring cyclic sulphonates and also sulphates—a phenomenon also found in the corresponding cyclic phosphonates whose observed rate enhancements prompted these studies.

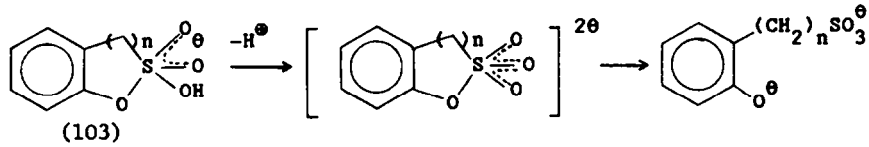
The observed rate enhancements for the cyclic compounds compared to their acyclic analogues can be understood, since there is need for relatively little perturbation of the bond angle of sulphur in the 5-membered ring sultones (and sulphates) to achieve the required transition state geometry (see below). The smaller rate enhancement for the 6-membered ring sultone is consistent with the increase of 5.3° in bond angle at sulphur.

As a probe for the transition state for hydrolysis of the 5-membered ring sultone **7**, kinetic studies for 5-substituted derivatives of **7** were carried out. A linear relationship between $\log k$ and the Hammett para substituent constants was observed for the sultones (excluding **8** and **97**) shown in Table 10. The observed ρ value of $+1.23$ indicates that electron withdrawing substituents accelerate the hydrolysis, and suggests that the S—O bond is significantly cleaved in the transition state.[116]

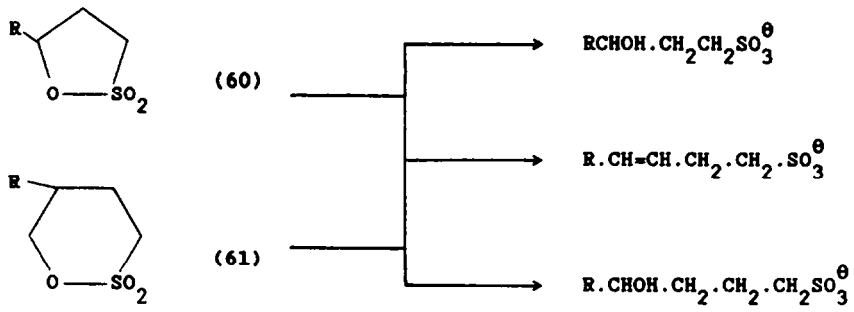
It has not been definitely established whether the reaction proceeds *via* a pentacoordinate intermediate (**103**) or directly via a transition state resembling **103** (Scheme 32), but with only partial bonding between sulphur and its apical substituents. The evidence is discussed in some detail by Kaiser and Kézdy.[120]

Reversible formation of the pentacoordinate intermediates **103** at first sight seems unlikely, since no significant isotope exchange was observed in studies on **7** and **8** with ^{18}O enriched base.[123] However, it is conceivable that the oxygen atoms external to the ring do not equilibrate during the lifetime of **103**. The lack of ^{18}O exchange can be understood if the trigonal bipyramidal configuration of **103** is such that the oxygen and carbon atoms of the sultone ring occupy one apical and one equatorial position. The conformer in which two negatively charged atoms occupy equatorial positions (i.e. **103**) should be substantially favoured over those in which these atoms occupy an apical and an equatorial position (i.e. **104**, Scheme 32). Thus pseudorotation from **103** to **104**, which would be required for ^{18}O exchange, may not be competitive with ring cleavage.

If **103** is an intermediate, it is conceivable that ring cleavage might involve prior ionisation of the hydroxyl group (Eq. 24). If, so the rate equation should contain a kinetic term second order in hydroxide ion. Studies with **8** and **98** show no such dependence,[115] indicating that if **103** is an intermediate it decomposes without prior ionisation.



(103) (24)



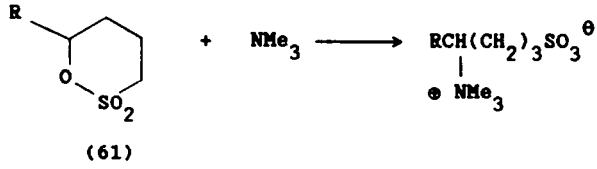
Scheme 33. Surfactants from hydrolysis of long chain alkane-1,3- and -1,4-sultones.[77]

4. INDUSTRIAL APPLICATIONS OF SULTONES

Two types of sultone are encountered most frequently in industrial applications: long chain alkane-1,3- and 1,4-sultones (**60** and **61**, respectively) and propane-1,3-sultone (**29**), usually referred to simply as propane sultone.

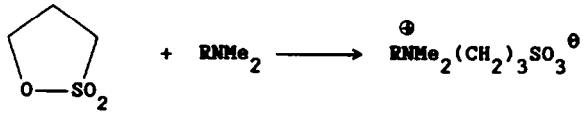
The major industrial importance of long chain alkane sultones is as intermediates in the manufacture of alpha olefin sulphonate (AOS), which is used as a surfactant in detergent products. In AOS manufacture a long chain olefin is treated with sulphur trioxide (*cf* Scheme 22), producing a mixture of alkene sulphonic acids and alkane-1,3- and 1,4-sultones[124,125] (**60** and **61** respectively). The former are neutralised and the latter are hydrolysed, usually under alkaline conditions, to give surface active alkene sulphonates and hydroxy alkane sulphonates,[77] as shown in Scheme 33.

Other surface active agents can be prepared from **60** and **61**, for example sulphobetaines, by reaction of tertiary amines[126,127] or pyridine[127] (Eq. 25).



(61) (25)

Sulphobetaines can also be prepared from propane sultone (**29**) and long chain alkyldimethylamines,[5] as shown in Eq. 26.

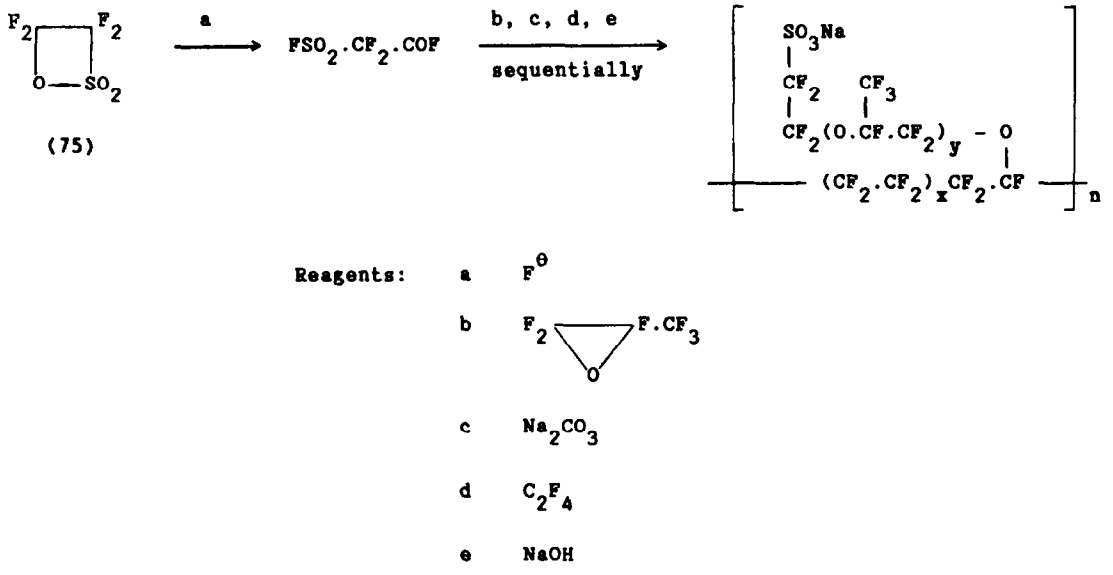


(29) (26)

Propane sultone is an extremely reactive sulphopropylating agent and there are many patents covering its use to modify surface properties of a variety of substrates. Cellulose, cellulose acetate and polyacrylonitrile (after hydrogen sulphide treatment) have been "alkylated" for the production of cation-exchange resins.[128] Cation exchange fibres have been made by hydrolysis of an acrylamide-acrylonitrile-vinyl chloride copolymer followed by treatment with propane sultone.[129] Hydrophilic coatings with increased wetting properties have been made from propane sultone treated cellulose esters.[130] Sulphopropylation has been used to increase dyeability.[131] Many other materials have been modified by propane sultone, producing fungicides,[132] fire-resistant polymers,[133] lubricating oil additives[134] and emulsifying agents.[135] Propane sultone has also been used to produce copolymers by reaction with ethylene imine and derivatives[136] and as a protein modifier.[137]

The applications of propane sultone are the subject of a 1973 review by Takasa.[138]

Tetrafluoroethane sultone (**75**), made by sulphonation of tetrafluoroethylene, is used as an

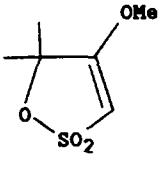


Scheme 34. Manufacturing route for perfluorosulphonate polymers used in ionomers.[139]

intermediate in the manufacture of perfluorosulphonate polymers used in ion exchange membranes (ionomers)[139] (Scheme 34).

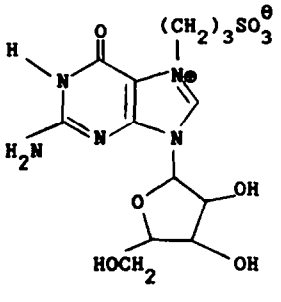
5. BIOLOGICAL PROPERTIES OF SULTONES

Most of the literature on biological properties of sultones is concerned with toxicological properties. However, the β-keto-γ-sultones and their enol ethers, as well as the analogous sultams, are claimed in a 1976 patent[62] to have cellular immunosuppressive properties which could make them useful therapeutic agents for inhibiting transplant rejection and in treating autoimmune disorders. Biological test data are given for one of the fifty compounds whose preparation is described in the patent, 5,5-dimethyl-4-methoxy-5H-1,2-oxathiol-2,2-dioxide (**53**) whose synthesis is shown in Schemes 15 and 16 (Section 2.3).

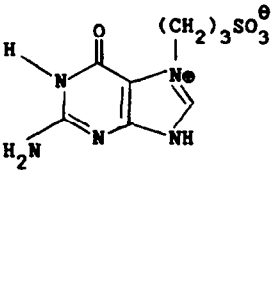


(53)

Propane-1,3-sultone (**29**) has been shown, in *in vitro* studies, to sulphoalkylate DNA from various sources, and also to react with guanosine and 2'deoxy-guanosine to yield the N-7 sulphopropyl nucleoside (**105**) and purine **106** (the deoxyribose moiety being presumed to be lost by solvolysis during work-up), respectively.[140]



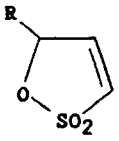
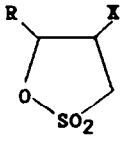
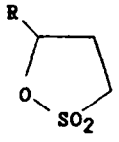
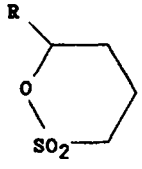
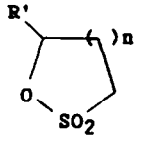
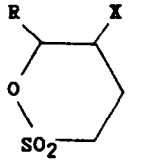
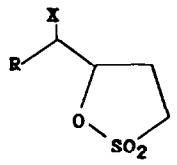
(105)



(106)

Both propane-1,3-sultone (**29**) and butane-1,4-sultone (**2**) are mutagenic,[141] **29** being about 41 times as potent as **2**. This difference in potency has been correlated with the difference in reactivity towards nucleophiles in aqueous solution, **29** being about 39 times as reactive as **2**[142] (*cf* the relative reactivities for hydrolysis, as discussed in Section 3.1.3. **29** is reported as being 37 times[86] or 50

Table 12. Behaviour of sultones in sensitisation tests[147]

Sultone	Sensitising properties	Cross reactivity
 (48)	Highly potent (R ranging from C_3H_7 to $C_{13}H_{27}$)	Cross-react with 49
 (49) (X = Cl, Br)	Highly potent (R ranging from C_7H_{15} to $C_{13}H_{27}$)	Cross-react with 48
 (60)	Moderate sensitisers (R=$C_{11}H_{23}$ and $C_{13}H_{27}$)	Cross-react with 61, but not with 49
 (61)	Moderate (R=$C_{12}H_{25}$) Weak (R=C_2H_5)	Cross-react with 60, but not with 49
 n=1,2	Very weak (R=C_8H_{17}, R'=$C_{8-n}H_{17-2n}$)	
 X=Cl, Br, OH	No evidence for sensitisation	
	(R=$C_{12}H_{25}$)	

times[7] as reactive as **2**). Both sultones have been found to be carcinogenic in studies on rats, **2** being much less potent than **29**.[143] Long term carcinogenicity testing in rats has revealed no carcinogenic properties with hexadecane-1,4-sultone (**61**, R = $C_{12}H_{25}$).[144]

The skin sensitisation properties of sultones have been investigated in some depth. Skin sensitisation involves a cell-mediated immune response to foreign (i.e. antigenic) macromolecules. Low molecular weight compounds which sensitise do so by interacting with skin proteins so as to render them antigenic. In most cases this interaction is through covalent binding resulting from attack by nucleophilic groupings on the proteins.[145]

The 1-alkene-1,3-sultones (**48**) and their precursors the 1-haloalkane-1,3-sultones (**49**, X = Br or Cl) are highly potent skin sensitisers.[104,146] Sultones **49** are believed to give rise to sultones **48** in the skin, since the two sultone types are mutually cross-reactive, i.e. animals sensitised to **49** respond positively to challenge by **48** and *vice-versa*.[104,146] Alkane-1,3- and 1,4-sultones, **60** and **61**, respectively, are also sensitisers: the 1,3 isomers (**60**) are the more potent but both types are much less potent than **48** and **49**.[104] Sultones **60** and **61** are mutually cross-reactive, but are not cross-reactive with the unsaturated sultones **48** and their precursors **49**. These cross-reactivity differences have been rationalised in terms of the different types of reaction which the sultones undergo with primary amines (see Sections 3.1.6 and 3.2.2) and, by inference, with biological nucleophiles.[104]

The behaviour of these and related sultones in sensitisation tests is summarised in Table 12 based on a paper by Roberts and Goodwin.[147]

The extensive sensitisation test data on sultones **60**, **61** and **48** for various chain lengths and test dosages have been used by Roberts and Williams[148] to verify a mathematical model whereby sensitisation potency as determined in animal tests is correlated with a Relative Alkylation Index (RAI):

$$\text{RAI} = \log [kD/(P+P^2)]$$

where k is the rate constant for reaction with *n*-butylamine under standard conditions, D is the sensitising dose administered, and P is the partition coefficient between methanol/water and hexane.

6. CONCLUSIONS

There have been many new developments in sultone chemistry since the last general review of the area[4] was published in 1954. Several of these developments have had, or promise to have, an impact in wider fields. One example is provided by the work of Bordwell *et al.*[18-29] culminating in a paper[26] which has made a major contribution to the understanding of the effects of ring substitution on ring opening and closing reactions in general. Among other fields where sultone chemistry is making a contribution is that of structure—biological activity relationships, particularly in relation to carcinogenicity[140-143] and contact dermatitis,[146,148] and current research into the role of β-sultones in olefin sulphonation[41-49] promises to have general implications for the theory of cycloaddition reaction mechanisms.

It can be predicted with some confidence that it will not be long before some sections of the present review become out of date.

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