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SOME ASPECTS OF THE ORGANIC CHEMISTRY OF SULPHUR (VI) DERIVATIVES.

by

Jeffrey Hoyle.

Submitted in partial fulfillment of the requirements for the Degree of Doctor of Philosophy at Dalhousie University, July 1984.

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Dedicated to the memory of my mother.

'There are things that are known
and things that are unknown;
in between the doors'

William Blake.

TABLE OF CONTENTS.

	Page
CERTIFICATE OF EXAMINATION	ii
COPYRIGHT AGREEMENT	iii
DEDICATION	iv
LIST OF TABLES	ix
LIST OF FIGURES	xi
ABSTRACT	xiv
LIST OF ABBREVIATIONS	xv
ACKNOWLEDGEMENTS	xvi
CHAPTER 1: GENERAL INTRODUCTION	1
PART I: ELECTROPHILIC REACTIONS OF SOME SULPHUR (VI)-CONTAINING HETEROCUMULENES WITH ELECTRON-RICH AROMATIC COMPOUNDS	6
CHAPTER 2: INTRODUCTION - HETEROCUMULENES	7
Sulphenes	8
Azasulphenes	14
Sulphur trioxide	23
CHAPTER 3: RESULTS AND DISCUSSION	29
Reaction with 2,6-dimethoxypyridine	30
Reaction with 1,3-dimethoxybenzene	36
Reaction with dimethylamino-substituted aromatics	42
Reaction with pyrroles	59

TABLE OF CONTENTS (Cont.)

Page

An alternative route to the biphenyl derivative **68** and similar species..... 62

Reactions of substituted sulphenes..... 71

Phenylsulphene reactions..... 72

Methylsulphene reactions..... 73

Reactions of azasulphenes..... 75

Reactions of ethylazasulphene..... 77

Reactions of carboalkoxyazasulphene..... 79

Reactions of sulphur trioxide..... 81

Suggestions for further work..... 85

PART II: CONCERNING THE SYNTHESIS AND PROPERTIES OF SOME β-KETOSULPHONES AND THEIR DERIVATIVES..... 86

CHAPTER 4: INTRODUCTION - β-KETOSULPHONES..... 87

β-Ketosulphides, sulphoxides and sulphones..... 87

Sulphenylation of compounds with active methylene groups..... 94

Highly substituted methanes with multiple electron-withdrawing groups..... 100

Carbon acids..... 102

Aims of the present study..... 111

TABLE OF CONTENTS (cont.)

Page

CHAPTER 5: RESULTS AND DISCUSSION..... 112

Preparation and spectral properties of β-ketosulphones and their derivatives.... 114

Reactions of a β-ketosulphone dianion.... 137

Reactions of the carbonyl group of β-ketosulphones and some of their derivatives..... 152

pK_a values of some β-ketosulphones and their derivatives..... 154

Summary..... 168

Suggestions for further work..... 168

PART III: NUCLEAR MAGNETIC RESONANCE OF THE SULPHUR-33 NUCLEUS IN SULPHONES..... 171

CHAPTER 6: INTRODUCTION -- SULPHUR-33 NMR..... 172

Historical..... 172

Nuclear magnetic resonance Group VI nuclei..... 176

Sulphur-33 nuclear magnetic resonance spectroscopy..... 179

CHAPTER 7: RESULTS AND DISCUSSION..... 189

Choice of reference compound..... 193

TABLE OF CONTENTS (cont.)

Page

Comparison of the results obtained in this study with carbon-13 data..... 194

Presentation of the correlations..... 204

Correlation of sulphur-33 chemical shifts with oxygen-17 data..... 206

Discussion of the correlations..... 207

Summary..... 213

Suggestions for further work..... 214

PART IV: EXPERIMENTAL, APPENDICES AND REFERENCES..... 215

CHAPTER 8: EXPERIMENTAL..... 216

General..... 216

Materials..... 218

Sulphur-33 nuclear magnetic resonance spectra..... 219

pKa measurements..... 220

Vacuum assisted chromatography..... 222

Preparation of compounds..... 222

APPENDIX I..... 298

APPENDIX II..... 304

APPENDIX III..... 312

APPENDIX IV..... 320

REFERENCES..... 325

LIST OF TABLES.

Table	Page	
I	27	Sulphonation of reactive heterocycles with sulphur trioxide complexes.
II	50	Results of the study of the reaction of N,N-dimethylaniline with sulphene.
III	82	Yields obtained in the aromatic sulphonation reactions.
IV	104	pK_a values of some carbon acids.
V	110	pK_a values of some β-ketosulphones
VI	136	Some mass spectral data for β-ketosulphones.
VII	144	^1H NMR results for 2-benzoylthiane-1,1-dioxide, **155**, in $CDCl_3$ at 25°C.
VIII	145	^1H NMR results for 2-chlorothiane-1,1-dioxide, **157**, in $CDCl_3$ at 25°C.
IX	155/6	Experimentally determined pK_a values in 50:50 ethanol-water at 30°C.
X	162	Correlations of the pK_a values of some carbon acids with σ^*
XI	178	Isotopes of the Group VI elements.
XII	182	Chemical shifts after Retcofsky and Friedel.[251]
XIII	184	Sulphur-33 nmr data after Faure et al.[254]

LIST OF TABLES (cont.)

Table	Page	
XIV	186	Sulphur-33 chemical shift data after Harris and Evans.[255]
XV	187	Sulphur-33 nmr data after Annunziata and Barbarella.[256]
XVI	191/2	Sulphur-33 data for twenty-seven sulphones.
XVII	195	Comparison of sulphur-33 chemical shifts obtained in this study with those of Harris and Evans.[255]
XVIII	199/200	Sulphur-33 and carbon-13 chemical shift data for twenty-seven related compounds.
XIX	208	Oxygen-17 and sulphur-33 chemical shifts for simple ethers and sulphones.
XX	221	Results of pK_a determination of **167**.

LIST OF FIGURES

Figure	Page	
I	34	Structure of the potassium salt of bis(methylsulphonyl)-3-(2,6-dimethoxypyridyl)sulphonylmethane, **51**.
II	38	Structure of bis(methylsulphonyl)-4-(1,3-dimethoxyphenyl)sulphonylmethane, **55**.
III	45	Calculated carbon-13 chemical shifts for **62** and **63**.
IV	53	The aromatic region of the proton nmr spectrum of fraction D at 360 MHz.
V	55	Calculated carbon-13 chemical shifts for model compounds to simulate **67** and **68**.
VI	68	The aromatic region of the proton nmr spectrum of 2,4'-bis(dimethylamino)-biphenyl; **77**.
VII	70	Compounds **78-82**.
VIII	125	Aromatic region of the carbon-13 nmr spectrum of **144** at 18°C.
IX	126	Aromatic region of the carbon-13 nmr spectrum of **144** + 1 equivalent of triethylamine at 18°C.

LIST OF FIGURES (cont.)

Figure	Page	
X	128	Aromatic region of the carbon-13 nmr spectrum of **144** + 1 equivalent of triethylamine at -60°C.
XI	129	Aromatic region of the carbon-13 nmr spectrum of **144** + 3 equivalents of triethylamine at -60°C.
XII	131	X-ray structure for **141**.
XIII	143	The aliphatic region of the proton nmr spectrum of **155**.
XIV	147	Proton nmr resonance of H-2 in **155**.
XV	148	Proton nmr resonance of H-2 in **157**.
XVI	164	pK_a values of β-ketosulphones in the SAP series versus σ^*.
XVII	174/5	The first proton nmr spectrum showing resolution of protons in different chemical environments.
XVIII	190	Examples of sulphur-33 nmr spectra obtained in this study.
XIX	201	A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure **194**.
XX	202	A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure **195**.

LIST OF FIGURES (cont.)

Figure	Page	
XXI	203	A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure **196**.
XXII	209	A plot of sulphur-33 versus oxygen-17 chemical shift values for simple ethers and sulphones.
XXIII	223	A plot of pH versus volume of base added for **167**.
XXIV	224	A plot of $1/\Delta$ pH versus volume of base added for **167** (Gran plot).
XXV	313	X-ray structure for the unit cell of **141**

The electrophilic substitution of aromatic compounds with sulphur trioxide has been known for 150 years. In the present work this reaction is extended to include a detailed study of the reactions of highly activated aromatic compounds, such as N,N-dimethylaniline, with sulphene ($CH_2=SO_2$) and with azasulphene ($HN=SO_2$) and derivatives. Sulphonamides may be synthesised in high yields, under mild conditions, by the hydrolysis of the aryl - carboalkoxy-azasulphene products.

A new, albeit low-yield synthesis of some biphenyls with novel substitution patterns is also described.

A new series of β-ketosulphones and some derivatives, especially those sulphenylated α to the carbonyl group, have been prepared and identified. Alkylation of the dianion from a β-ketosulphone has provided a new, facile high-yield synthesis of substituted thiane-1,1-dioxides. A detailed proton nmr study showed that 2-chloro- and 2-benzoyl- thiane-1,1-dioxide exist in deuterochloroform solution primarily with the 2-substituent in the axial orientation. Such a conformational preference in cyclic sulphones arising from polar rather than steric forces is quite unusual.

The carbonyl group in a β-ketosulphone shows reactivity like that of a simple ketone whilst the same group in the monosulphenylated derivatives and their oxidation products does not undergo such reactions.

The pK_a values of nineteen β-ketosulphones have been measured and these have been correlated with σ^* as have other carbon acid data available in the chemical literature.

Sulphur-33 nmr chemical shifts and linewidths of twenty-seven sulphones have been measured; the data obtained in this study are consistent with those published to date. There is a good correlation of sulphur-33 versus carbon-13 chemical shift data for symmetrical dialkyl sulphones and correlations with two other structural types do exist, but are not as clearly defined.

LIST OF ABBREVIATIONS.

decomp.....decomposes.

DMK.....acetone.

exch.....exchangeable.

Me, me.....methyl.

pht.....phthalimido.

All other abbreviations and symbols used are standard notation.

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Finally, I am forever indebted to my wife Nicki not only for the typing and preparation of this thesis but also for everthing that she gave up in order for me to be able to complete this work. I love you darling...

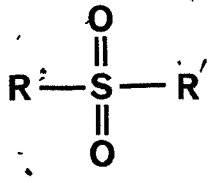
CHAPTER 1

GENERAL INTRODUCTION

Many chemists associate sulphur-containing organic molecules with unpleasant smells. Notwithstanding this, organosulphur chemistry has been studied for well over a hundred years, there being a wide range of naturally occurring and coal-tar-derived organic compounds that contain sulphur, e.g. cysteine, thiophene, etc. During the last few decades an increasing volume of organic syntheses involving the use of sulphur-containing compounds has been published. Much of this work concerns the introduction of a sulphur moiety as a control element which is then removed at a later stage.

In this thesis some new advances in the chemistry of organosulphur compounds, principally concerning sulphones, is presented and this first chapter briefly reviews the established properties of sulphones. Since there are many excellent reviews [1-7] on this subject, only the key points will be outlined here.

A sulphone is generally represented by structure 1,



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where R and R' can be a wide range of substituents bonded through carbon. There have been many studies,[3] both theoretical and experimental, to try to establish the nature of the bonding both within the sulphone group itself and also with the attached substituents. In former years there were two mutually exclusive beliefs, one assuming the involvement of d-orbitals in bonding, the other not. This dichotomy was caused by the phenomenon of 'octet expansion' of third row-elements believed by some to involve the use of d-orbitals. Currently, it is generally believed that the bonding is somewhere between the two extremes although a final agreement has not yet been reached.[8]

Sulphones are blessed with high thermal and chemical stability but it is this fact which has led to their relative neglect until recent times; stable species do not make good versatile intermediates in organic synthesis.

Although some sulphones occur naturally, e.g. dimethyl sulphone occurs in cows blood, most have to be synthesised. Sulphones are normally prepared by one of three routes i.e.

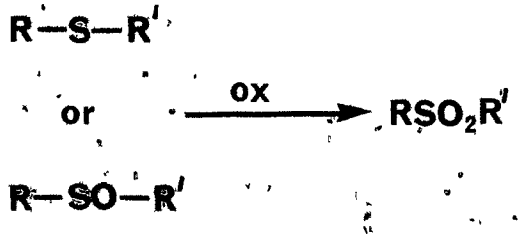
a) oxidation of sulphides or sulphoxides

b) reaction of alkyl halides with sulphinates or sulphites

c) Friedel-Crafts reactions.

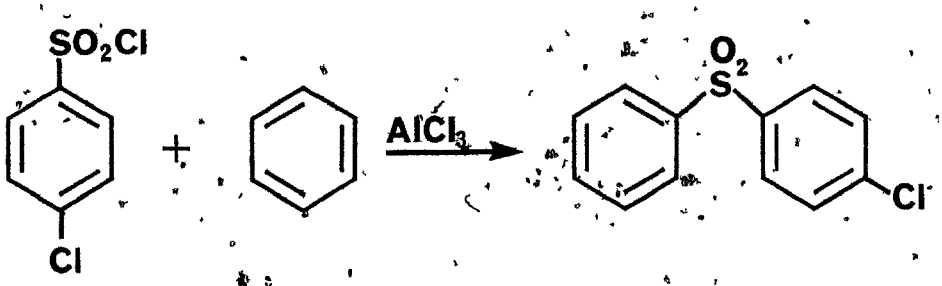
There are however many other methods used that lack generality,[3] including additions to multiple bonds, rearrangements, cycloadditions *etc.*

Oxidation of sulphides and sulphoxides to sulphones is the simplest preparative method and can be brought about by many common oxidising agents such as hydrogen peroxide and potassium permanganate. It is interesting



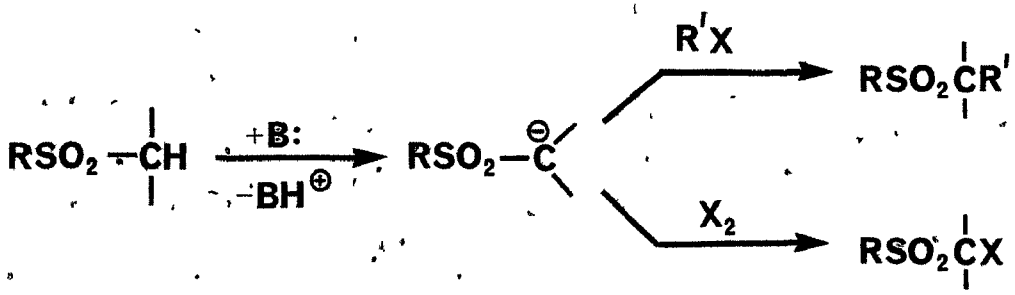
to note that the reverse reaction, reduction of a sulphone, is much more difficult but can be effected in certain cases by using $LiAlH_4$, amongst other compounds. Alkylation of sulphinate salts with alkyl halides and other related species is generally a high-yield method used especially to prepare aryl sulphones, *e.g.*

The Friedel-Crafts reactions of sulphonyl chlorides with aromatic compounds have been used to prepare mainly diaryl sulphones, *e.g.*

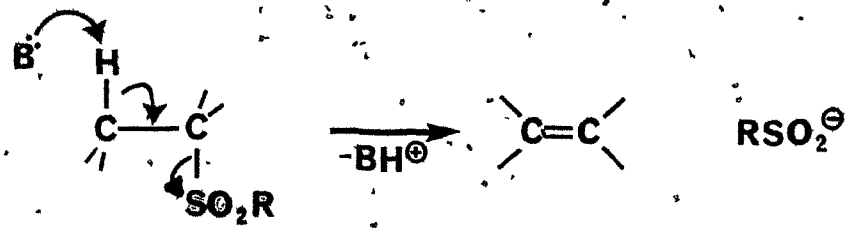


Of the other methods used to prepare sulphones the reaction of sulphenes with enamines and related compounds is of importance to the current study; this will be discussed in some detail in the next chapter.

Sulphones are completely unaffected by all but the strongest acids; their most important reaction involves the use of a base to remove one (or more) of the relatively acidic protons attached to a α-carbon atom. The carbanion thus formed is stabilised by the electron-withdrawing sulphone group and undergoes all the regular carbanion reactions such as alkylation, halogenation etc.



Sulphinic acids are relatively good leaving groups and hence many sulphones are prone to base-catalysed 1,2-eliminations. The sulphone group may also be exchanged



for a hydrogen atom by reductive elimination with various reagents and methods, e.g.

$$PhCH_2SO_2CH_2COCH_3 \xrightarrow[MeOH]{h\gamma} CH_3COCH_3$$

Sulphones are readily identified using infra-red spectrophotometry. They exhibit two strong bands in the regions 1380-1300 cm^{-1} and 1170-1130 cm^{-1}, for asymmetric and symmetric stretching, respectively,[9] and given their lack of chemical reactivity this is the only available general method of identification.

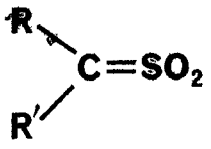
PART I

ELECTROPHILIC REACTIONS OF SOME SULPHUR (VI)-CONTAINING HETEROCUMULENES WITH ELECTRON-RICH AROMATIC COMPOUNDS.

CHAPTER 2

INTRODUCTION - HETEROCUMULENES

Heterocumulenes are compounds which possess adjacent π-bonds where one or more of the atoms in the π-system are heteroatoms, for example sulphur, nitrogen or oxygen. These species command much general interest from organic chemists since they are commonly found to be useful as reactive intermediates in synthesis. In the present study sulphenes,* azasulphenes* and sulphur trioxide (structures **2**, **3** and **4** respectively) are the three heterocumulenes of interest.



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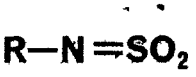

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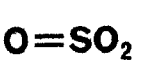

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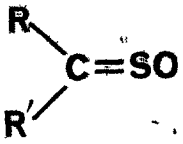
* These names are the ones used throughout this thesis. The current IUPAC and Chemical Abstracts Service nomenclatures are: thioformaldehyde dioxide and methanethial, S,S-dioxide for sulphene with N-sulphonylamine and sulphimide for azasulphene. These names are rather unwieldy especially when substituents are present and so are not used here.

Sulphenes

Sulphenes are well established as reactive electrophilic intermediates although to date no stable monomeric sulphene has been isolated, this is in marked contrast to the related species sulphine, 5, for which



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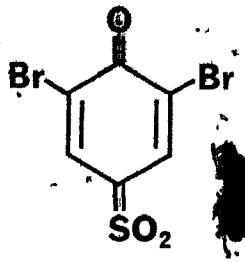
several structural modifications have been isolated as crystalline solids.[10]

Zincke and Brüne[11] first proposed the existence of a sulphene-type structure. They attributed the yellow colour of a reaction mixture, formed from the reaction of the corresponding sulphonyl chloride, to a species with structure 6. The term 'sulphene' was first used



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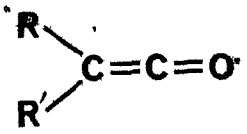
three years later in 1911 by Wedekind and Schenk.[12] This choice of name was rather unfortunate, it indicates a

formal relationship with ketene, 7, rather than



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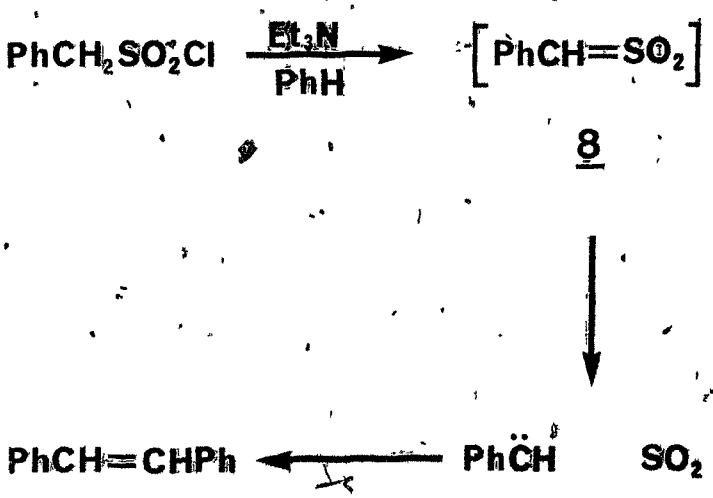
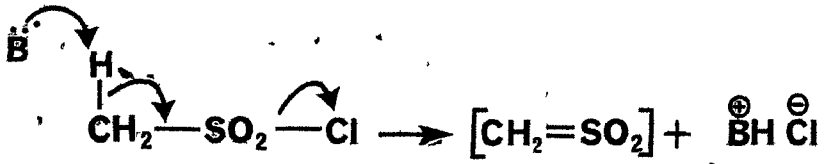
indicating the oxidation level of the sulphur atom. The latter method is the generally accepted one for organic sulphur nomenclature.[2] Wedekind and Schenk had planned to isolate the generated sulphene but were unsuccessful. They were however able to identify the products which were assumed to result from the decomposition of phenylsulphene, 8, viz.



Since this initial work, several groups of workers, most notably those led by King, Opitz and Truce, have published much work regarding the generation and reactions of sulphenes, mostly during the past two decades.

Sulphenes are most often generated by the reaction of a sulphonyl chloride possessing at least one α-hydrogen atom with a base such as triethylamine. The resulting dehydrochlorination of the sulphonyl chloride leads to the production of a sulphene *viz.*



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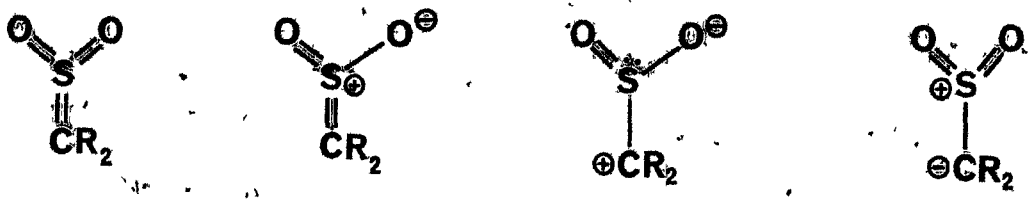
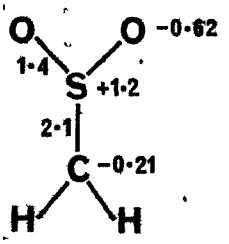
There are many other methods used for the generation of sulphenes, including the reaction of diazoalkenes with sulphur dioxide and the fragmentation of α-haloalkane sulphinate anions by photolysis or thermolysis. These methods and others have been eloquently discussed by King[14] and the reader is directed to this review for more details.

There are several possible canonical structures for sulphenes and normally these are depicted by structure **10**. However, in general, sulphenes are probably



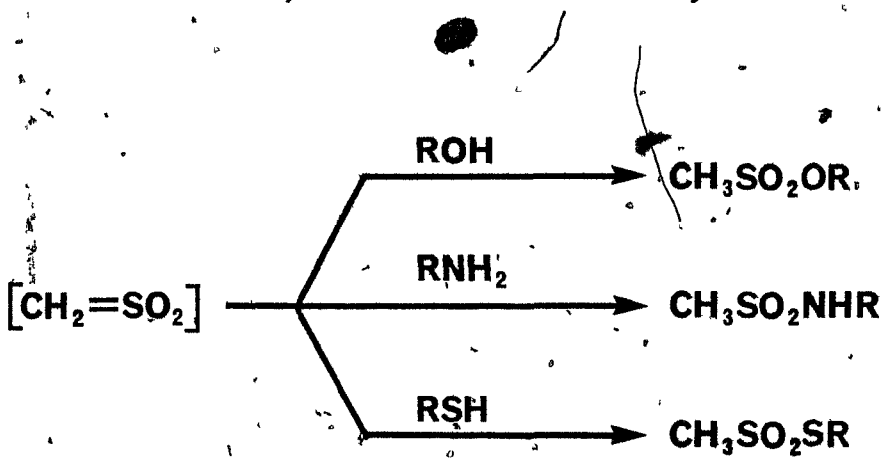
10 **11** **12** **13**

best described by a canonical form which has only one sulphur-oxygen double bond with positive charge on sulphur and a negative charge on oxygen, that is structure **11**, there being two such structures of equal energy. Further possible canonical structures such as **12** and **13** may also be drawn where **12** shows carbonium ion character on the α-carbon atom whilst **13** shows carbanion character. Semi-empirical molecular orbital calculations[15] have shown that sulphene should have the following structure and charge distribution:

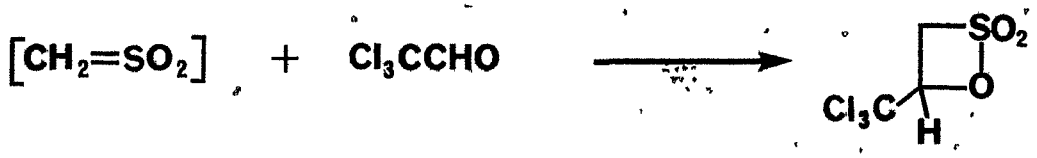


i.e. that structures **11** and **13** are the main contributors. These data are in concordance with the normal mode of reaction of sulphene, i.e. that the sulphur atom is electrophilic.

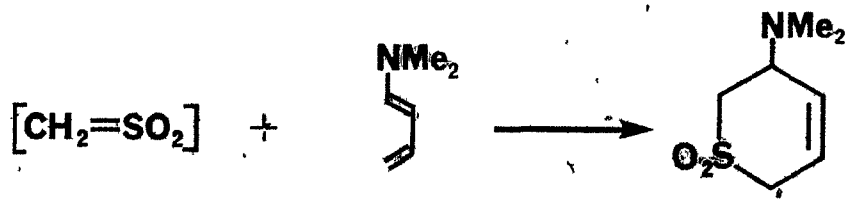
The most common reaction of sulphene and its derivatives is simply addition of nucleophiles to the formal carbon-sulphur double bond. This type of reaction occurs for a wide range of nucleophiles and these reactions are easy, clean methods of producing



sulphonate and thiosulphonate esters and sulphonamides. Sulphenes also undergo 2+2 cycloaddition reaction with electrophilic ketones and aldehydes e.g.

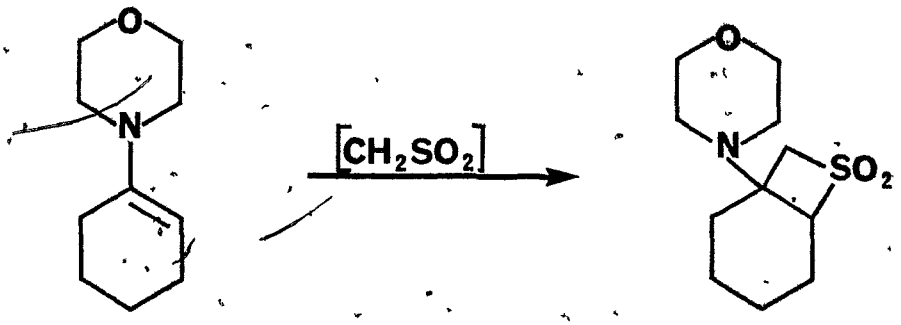


and 2+4 cycloadditions with activated dienes e.g.

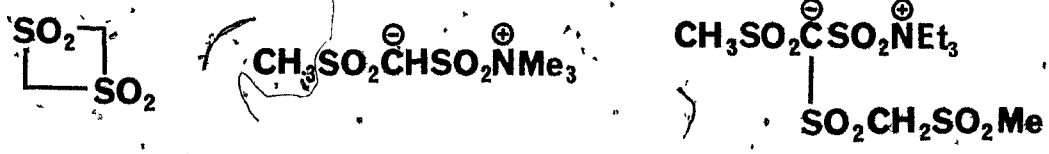


Probably the most useful reaction of sulphenes is the formation of thietan-S,S-dioxides which are otherwise relatively inaccessible. The reaction involves the combination of a compound which possesses an electron-rich carbon-carbon double bond, such as an enamine, with

sulphene as exemplified below.



The reaction of sulphene with itself has been studied by Opitz and co-workers and by Grossert and Bharadwaj. Opitz and Mohl[16] reported the isolation of a cyclic sulphene dimer, **14**, while Opitz and Bücher[17] isolated a dimer complexed with trimethylamine **15**.

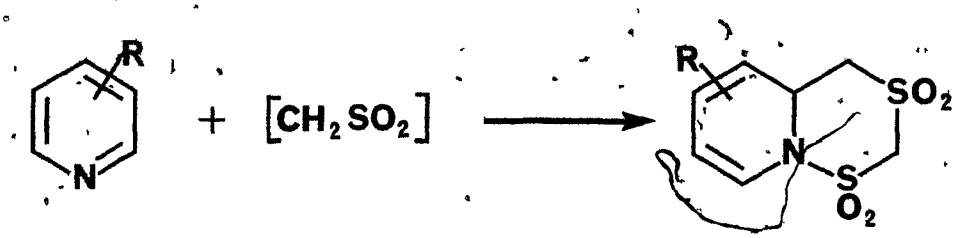


14 **15** **16**

Grossert and Bharadwaj [18] investigated the oligomerisation of sulphene in the absence of nucleophiles and found that a tetrameric species, **16**, may be produced as well as a dimer with a similar structure to that of **15**.

Sulphene has been shown by Grossert[19] to be capable of addition to pyridine and some of its 3-, 4- and 5-

substituted derivatives to form a 2:1 adduct containing a pyridodithiazine ring, **17**. However, it appears that 2- and 2,6- substituted pyridines either do not undergo such a reaction or that the product once formed, readily



17

decomposes. Grossert has shown that 2,6-dimethylpyridine (2,6-lutidine) yields no useful products by reaction with sulphene although a tarry residue is produced.[20]

The chemistry of sulphenes has been regularly reviewed[14,21-23] and the reader is directed to these references, particularly the most recent of these[14] for further details. One notable exception to the reactions quoted in all these reviews is that of electrophilic substitution by sulphene on aromatic compounds. This area is covered in the present study and no reports of such reactions have been published previously as far as the author is aware.

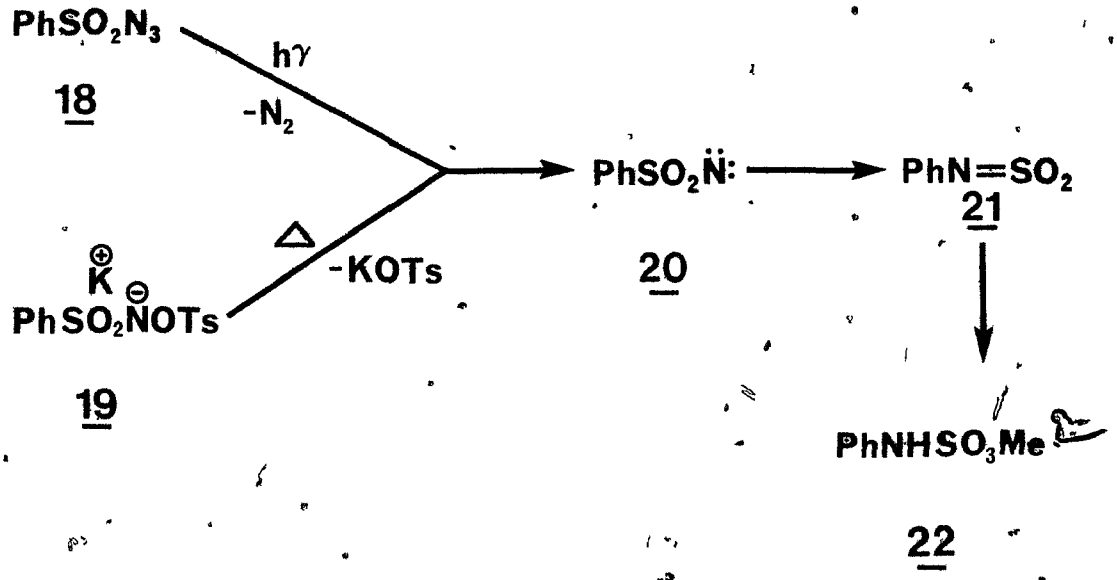
Azasulphenes

Azasulphenes, **3**, have been much less studied than sulphenes. They are reactive electrophilic intermediates

$$R-N=SO_2$$

3

and have been invoked in order to explain the products of several reactions, for example, the products of the Curtius and the Lossen rearrangements of compounds 18 and 19 respectively.[24] Decomposition of the nitrene, 20 giving phenylazasulphene, 21, is followed by addition of methanol producing methyl N-phenylsulphamate, 22.



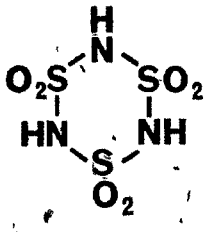
In a series of papers beginning in 1967, Burgess and co-workers[25] claimed to be the first to generate 'a new class of electrophilic amine derivatives designated as N-sulphonylamines'. This claim is quite erroneous since they failed to recognise the earlier work of Traube[26]

who postulated the formation of the parent azasulphene,* 23 from the reaction of sulphuryl chloride with ammonia.

$$HN{=}SO_2$$

23

Although Traube was unable to isolate azasulphene itself, a feat which still remains to be achieved, he claimed that the cyclic trimer, 24, and its silver salt, 25 had been isolated from this reaction. Later work



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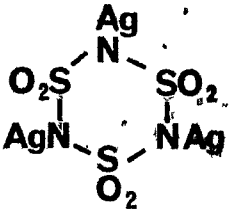


25

by Hantzsch and co-workers[27,28] indicated that the cyclic trimer could not be prepared in a pure state, but

---

* Unsubstituted azasulphene ($HN = SO_2$) has been commonly referred to as sulphimide in the literature. In this work it will be named azasulphene to be consistent with the nomenclature used for sulphene ($CH_2 = SO_2$).

could be isolated as the silver salt, **25**. Methylation of this salt with methyl iodide yielded a trimethyl derivative, **26**. Appel and co-workers[29,30] were able to

$$(SO_2{=}NMe)_3$$

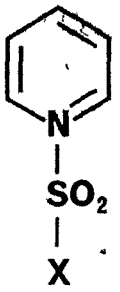
26

isolate long-chain polymers of azasulphene from the reaction of sulphuryl chloride with ammonia. They were, however, unsuccessful in attempts to obtain the cyclic trimer, **24**. In 1967, Appel and Helwerth[31] reported the isolation of 2:1 adducts of azasulphene and tertiary nitrogenous bases as exemplified by structure **27**. The adducts were obtained by the reaction of these bases with sulphamoyl chloride at -40°C. The structure of

$$2NH_2SO_2Cl + 3NR_3 \longrightarrow NH_2SO_2\overset{\ominus}{N}SO_2\overset{\oplus}{N}R_3$$

27

these adducts is similar to that of the sulphene-tertiary amine adducts first reported by Opitz and Bücher[17]. Appel and Helwerth[31] also suggested that they had isolated a rather unstable 1:1 adduct **28** of azasulphene with pyridine having a structure isoelectronic with that of the known pyridine-sulphur trioxide adduct, **29**.

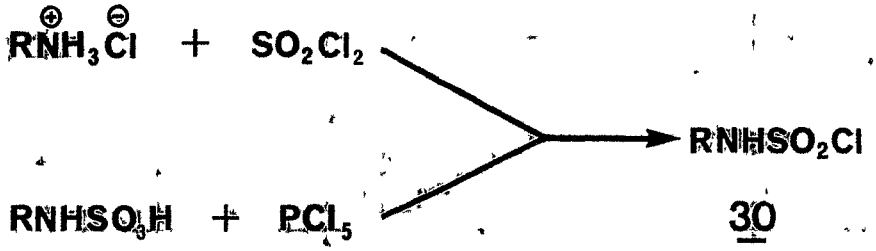


28 X = $\overset{\ominus}{N}H$

29 X = $O^{\ominus}$

Synthetic work involving substituted azasulphenes was indeed pioneered by Burgess and co-workers and most reactions of these reactive electrophiles have involved N-alkyl, N-benzoyl and N-carboalkoxy substituted derivatives.

Simple N-alkyl substituted azasulphenes have been prepared by dehydrochlorination of sulphamoyl chlorides, 30. These latter compounds have been synthesised either by reaction of sulphuryl chloride with amine hydrochlorides[32,33] or by the chlorination of sulphamic acids with phosphorus pentachloride.[34] The



first of these methods is limited to the preparation of only a few different derivatives since the amine hydrochlorides are not readily available in a pure state. The procedure is also subject to rather long reaction times and the use of large quantities of reagents. The second method does not suffer from these limitations because a wide-range of pure sulphamic acids may be prepared by the high-yield reaction of organic isocyanates with fuming sulphuric acid in nitromethane solution.

$$RNCO + H_2SO_4.SO_3 \longrightarrow RNHSO_3H$$

Carboalkoxyazasulphenes have also been generated by two routes. Atkins and Burgess[35] have reacted the sulphamoyl chloride, **31**, with a base; this type of

$$RO_2CNHSO_2Cl + base \longrightarrow RO_2CN{=}SO_2$$

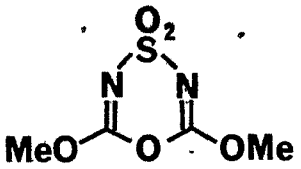
31

sulphamoyl chloride is best prepared by careful reaction of chlorosulphonyl isocyanate, **32**, with the required alcohol or phenol.[36,37] Burgess and Williams[38] on the

$$OCNSO_2Cl + ROH \longrightarrow RO_2CNHSO_2Cl$$

32

other hand have generated carbomethoxyazasulphene by the thermal fragmentation of the substituted 1,4,3,5-oxathiadiazine-S,S-dioxide, **33**.



33

$$\longrightarrow \quad MeO_2CN{=}SO_2 \; + \; MeCN$$

As with sulphenes, the most common synthetic use of azasulphenes is their reaction with nucleophiles such as primary amines[25] and alcohols.[35,39,40] The reaction with primary amines is straightforward and usually produces an unsymmetrical sulphamide such as **34** in high yield.

$$EtN{=}SO_2 \; + \; PhNH_2 \longrightarrow EtNHSO_2NHPh$$

34

The reaction with alcohols is more complex. Primary alcohols produce urethanes such as **35** in high yields.

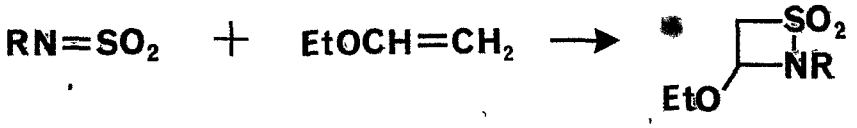
$$Et_3\overset{\oplus}{N}SO_2\overset{\ominus}{N}COOMe \; + \; n\text{-}BuOH \longrightarrow n\text{-}BuNHCOOMe$$

35

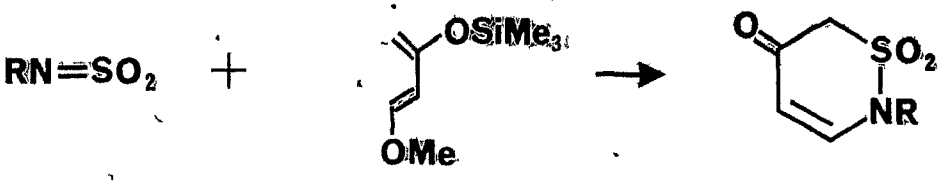
The reaction of secondary and tertiary alcohols which possess a hydrogen atom on the α-carbon atom produces an alkene by a stereospecific *cis* elimination mechanism.[41,42]

Azasulphenes also react with a wide-range of

activated alkenes producing 2+2 cycloaddition products.[2,43,44] Such ring systems are difficult to

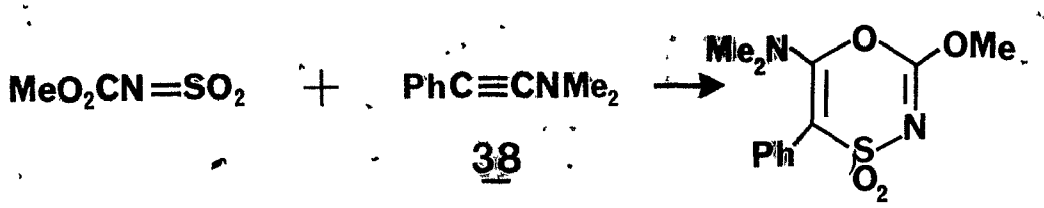


prepare by other synthetic routes. Kloek and Leschinsky[45] have reported the formation of 2+4 cycloaddition products from the reaction of N-alkylazasulphenes with activated dienes such as **36**.



36 **37**

1,2-Thiazinone dioxides **37** are also difficult to prepare by other methods. Since **37** could not be isolated prior to use of acidic work-up conditions, Kloek and Leschinsky reported that the cycloaddition reaction likely involved a step-wise mechanism. They have also shown[46] that carboalkoxyazasulphenes react with ynamines to produce novel heterocycles as exemplified by the following equation using **38**.



As far as the author is aware the only report of azasulphenes undergoing an aromatic electrophilic substitution reaction is due to Atkins and Burgess,[47] thus:

> 'The inner salt (39) was capable of electrophilic aromatic substitution of N,N-dimethylaniline and only the para isomer, N,N-dimethyl-N'-carbethoxysulfanilamide was produced. N-Sulfonylethylamine generated in the presence of N,N-dimethylaniline gave only N,N-dimethyl-N'-ethylsulfanilamide while N-sulfonylbenzamide (40) afforded the corresponding ortho- and para-substituted sulfanilamide in a ratio of 4:6 albeit in low yield.'

39

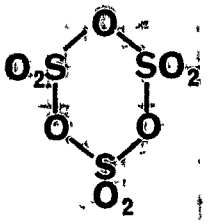
40

They made no further comment on this interesting

reaction

Sulphur trioxide

Freshly distilled sulphur trioxide, a 'water-white' liquid at room temperature and pressure, has been shown by Raman spectroscopy[48] to consist of approximately 90% of the trimeric form, **41**, and only 10% of the monomer itself. On standing with exposure to moisture, long-chain polymers, **42**, with some degree of cross-linking are spontaneously formed, although commercially available liquid sulphur trioxide is stabilised with various additives.



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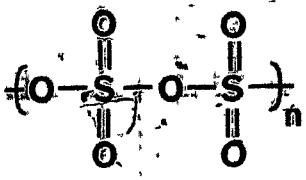


42

The reactions of sulphur trioxide, and its derivatives as reactive electrophilic species, are fairly well understood since they have been studied for about 150 years. Sulphonation, the introduction of a sulphonate group bonded to a carbon atom, is a very important large-scale industrial process. Sulphonation of benzene using sulphuric acid was, until relatively recently, the first step in the industrial production of phenol.[49] The introduction of a sulphonate

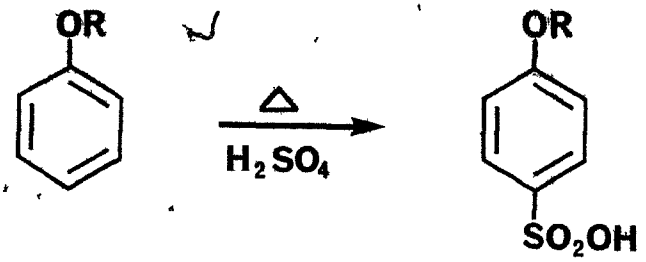
group expands the usefulness of many organic materials since this type of polar hydrophilic group greatly aids water solubility. This property has been exploited in the development of detergents, water-soluble dyestuffs, flavouring and medicinal compounds.[50,51]

Sulphonation of organic compounds may be brought about under a wide-range of conditions by several different reagents including sulphuric acid, oleum, chlorosulphonic acid, sulphamic acid, sulphur trioxide gas and organic complexes of sulphur trioxide. These methods and reagents have been discussed by Gilbert[52] and the reader is directed to this source for in-depth information. Since so much has been written concerning the sulphonation of organic compounds this section will deal only with the sulphonation of aromatic compounds as is relevant to the present study.

Nelson[53] has written a good review of aromatic sulphonation which covers the literature up to 1963. The old literature abounds with claims that have not been substantiated to date. As early as 1892, Moody[54] reported that a reinvestigation of some work due to Kekule showed that sulphonation of anisole (**43**,R=Me) and phenetole (**43**,R=Et) afforded only the *para*-substituted sulphonic acid, **44**, and not a mixture of *ortho* and *para* isomers as claimed by the original author.

Sulphonation with sulphur trioxide-Lewis base

adducts has been reviewed by Gilbert[55] and is the

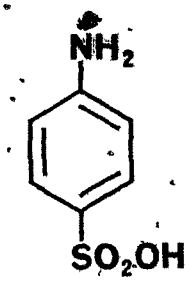


43 44

reaction most relevant to the present work. The bases commonly used in the formation of these adducts include tertiary amines such as triethylamine and pyridine and much weaker bases such as amides and ethers. Generally, the most stable complex is formed with the strongest base (whilst the most reactive adduct is formed with the weakest base). Hence an order of reactivity may be established (i.e. $SO_3.NR_3$ < SO_3.pyridine < SO_3.dioxane). These complexes are all solids at room temperature and are generally prepared by the careful interaction of the free base with sulphur trioxide or chlorosulphonic acid.[55] On reaction of a sulphur trioxide complex with an aromatic compound a salt ot a sulphonic acid is produced.

Generally, sulphur trioxide complexes have been of little practical use in the sulphonation of aromatic rings. Owing to the reduced reactivity of the sulphur trioxide moiety, only aromatic species that are highly

activated towards electrophilic aromatic substitution react and then only under rather forcing conditions. For example, aniline reacts with sulphur-trioxide-pyridine complex at 170°C to give sulphanilic acid, **45**,[56] whilst anisole reacts under similar conditions with sulphur trioxide-dioxane to give **46**.[57,58]



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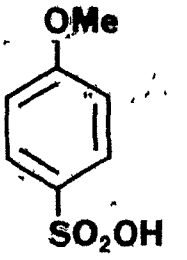
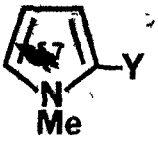
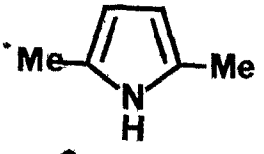
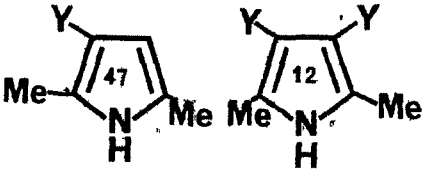
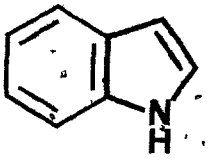
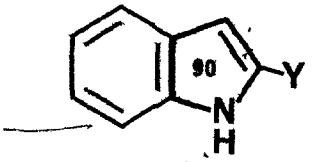
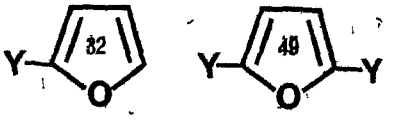
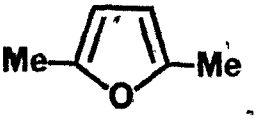
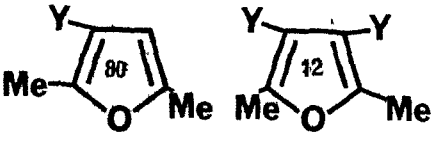
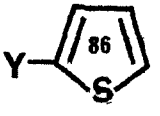
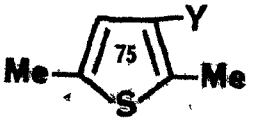
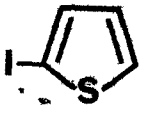
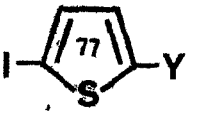


46

Thus the use of sulphur trioxide complexes in electrophilic aromatic substitution reactions has generally been restricted to reactions involving furan, pyrrole, indole, thiophene and their derivatives. Sulphonation of these rather reactive aromatic species still requires the heating of reaction mixtures to 80-150°C in a sealed tube in ethylene dichloride usually for many hours.[51,59] Table I gives a selection of such reactions. Although these conditions seem rather drastic they are exceedingly useful for reactive heterocyclic compounds since these species are usually thermally stable whereas the more acidic reagents, such as oleum, generally induce extensive decomposition or

Table I: Sulphonation or reactive heterocycles with sulphur trioxide complexes.

Substrate	Sulphonating agent	Product(s) (yields)	Reference
	P		60
	P		61
	P		62
	P		52
	P		59
	P/D		63
	P/D		64
	P		65

P = SO_3.pyridine, D = SO_3.dioxane, Y = SO_3H.

polymerisation. Yields in the reactions vary widely, from a few percent to nearly quantitative; di- and tri-sulphonic acids are often produced.[59]

In summary, the electrophilic aromatic substitution reaction of sulphur trioxide with aromatic compounds is very well established whilst a similar reaction for the related heterocumulenes sulphene and azasulphene and their derivatives is unknown with the exception of one cryptic reference.[47] The purpose of the current study is to investigate such a reaction for the sulphenes and azasulphenes and to draw the attention of chemists to the similarities of the chemistry of these three heterocumulenes.

CHAPTER 3

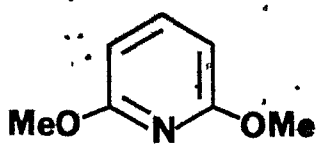
RESULTS AND DISCUSSION

The reaction of sulphene with electron-rich aromatic compounds was best carried out at -30° to -20°C in either dry acetonitrile or dry tetrahydrofuran under an atmosphere of dry nitrogen. At temperatures appreciably higher than these, the oligomerisation of sulphene, as reported by Grossert and Bharadwaj,[18,66] competed significantly and halted the formation of substitution products. Under more hydrous conditions there was usually little or no aromatic substitution product obtained and the starting sulphonyl chloride was hydrolysed to the sulphonic acid.

The sulphene used in these reactions was generated *in situ* usually by the dropwise addition of triethylamine in a solvent to a solution of the required aromatic compound and methanesulphonyl chloride. It should be noted that triethylamine was necessary for the successful isolation of products. Addition of the nucleophilic species (*i.e.* the aromatic compound) after first forming the sulphene resulted in much reduced yields, again due to competition by the oligomerisation reaction.

Reaction with 2,6-dimethoxypyridine.

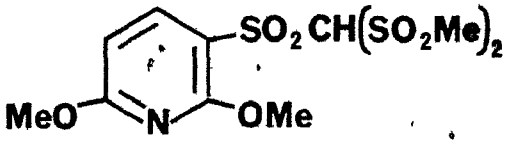
The initial nucleophile chosen was 2,6-dimethoxypyridine, **47**, for historical reasons since much



47

of the work concerning sulphenes studied in this laboratory has involved pyridine and its substituted derivatives. The use of 2,6-dimethoxypyridine in a reaction was novel since in-depth investigation of the literature revealed very little reported chemistry. Although 2,6-dimethoxypyridine is commercially available (Aldrich # D 13,700-6) its only apparent preparative use is in an early step in the synthesis of some compounds with useful insecticidal properties.[67] Very little basic chemistry of 2,6-dimethoxypyridine has been published; known reactions involve the bromination of the N-methylpyrylium ion[68] and nitration in strongly acidic media.[69]

An excess of sulphene reacted with 2,6-dimethoxypyridine to yield a 3:1 adduct whose structure was shown to be as depicted by **48**.



48

The structure was determined by various spectroscopic and other techniques. Since the formation of bis(methylsulphonyl)-3-(2,6-dimethoxypyridyl)-sulphonylmethane, 48, was a novel reaction, a thorough characterization was required. Infra-red spectroscopy indicated the presence of a sulphone group or groups (1340cm^{-1} and 1155cm^{-1}) and the presence of an aromatic residue. Proton nmr suggested the presence of two equivalent methylsulphonyl groups, two different methoxyl groups, a methine proton and two aromatic protons which exhibited an AB pattern. Carbon-13 nmr showed that there are nine different carbon atoms present with one resonance being due to two carbon atoms. Since all the aromatic carbon atoms are different, the sulphene residue must be in the 3-position of the pyridine ring, a fact confirmed by the proton and the carbon-13 nmr spectra which both showed two different types of methoxyl group. The mass spectrum of 48 showed a small peak at m/z 373(6%) which was assumed to be due to the molecular ion, a fairly large peak due to loss of a methylsulphonyl group at m/z

294(M-79) and the base peak at m/z 202 which was probably due to the pyridine residue with an attached SO_2 group. A molecular weight determination by proton nmr, using mesitylene as internal standard, gave a molecular weight of 354±20, which indicates that the product contains three sulphene units. Since sulphene oligomerises in a head-to-tail fashion[16-18] structures **49** and **50** are the two plausible part-structures for the sulphene residue, however, **49** is ruled out by the nmr evidence for two methylsulphonyl groups.

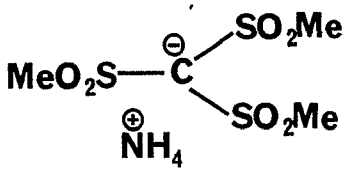
49 **50**

A CHS elemental analysis was consistent with an empirical formula of $C_{10}H_{15}NO_8S_3$.

All the evidence detailed thus far indicated the given structure, **48**, for the sulphene-2,6-dimethoxypyridine adduct. This was examined by X-ray diffraction methods, but the structure could not be solved. Thus the synthesis of a heavy metal salt of **48** was attempted. Although it proved impossible to prepare 'good' crystals of the rubidium or barium salts, such a crystal of the potassium salt (**51**, page 34) was made using a similar

method to that employed by Davoy et al.[70] X-ray diffraction was successfully used to determine the structure of this salt and a projection of the structure is presented in Figure I. It was also determined that there is one molecule of water per molecule of **51** present in the structure; this does not appear in the figure.

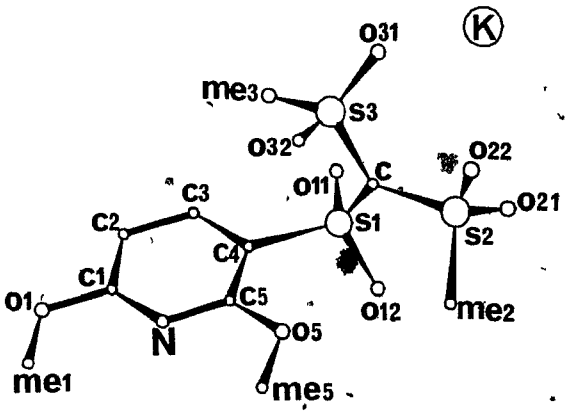
The structure of **51** is of particular interest since it confirms the difficult-to-obtain but much quoted results of Hoogsteen,[71] who found that the ammonium salt of tris(methylsulphonyl)methane, **52**, possessed a trigonal



52

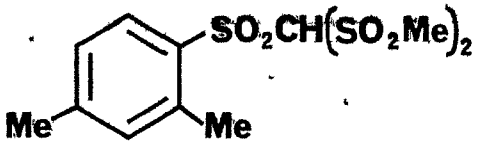
planar $C(SO_2)_3$ unit with S-C-S bond angles close to 120°. The average C-SO_2Me bond length in **51** is 1.718(8)Å which is a little longer than the corresponding bond lengths in **52**; however, this value is still shorter than the carbon-sulphur single bond length in dimethylsulphone (1.774(3)Å [72]). The sulphur-oxygen bond lengths in **51** are close to the normal single bond length (1.439(14)Å[73]), the average being 1.436(5)Å.

Figure I: Structure of the potassium salt of bis(methyl-sulphonyl)-3-(2,6-dimethoxy-pyridyl)sulphonylmethane, 51.



Complete X-ray diffraction data for the potassium salt of **51** are given in the Experimental section and in Appendix I of this thesis.

Since it seemed that the reaction of sulphene with 2,6-dimethoxypyridine was an electrophilic aromatic substitution, similar reactions were attempted on a series of aromatic compounds. The reactions of m-xylene and anisole with sulphene did not yield an isolable amount of product however, proton nmr spectra were run on very small quantities of product and these indicated that some reaction had occured. The aromatic region of the product from m-xylene seemed to indicate the presence of an ABX system and also two different methyl groups attached to an aromatic ring: for anisole the proton nmr indicated an AA'BB' system present in the aromatic region and a ratio of 2:1 for methylsulphonyl to methoxyl protons. It is thus suggested that **53** and **54** are formed respectively, based on the proton nmr evidence and the known structures of the other aromatic compound-sulphene adducts.



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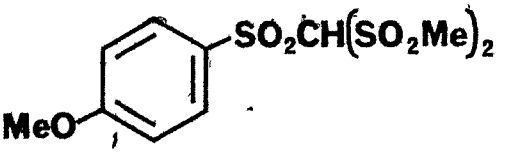
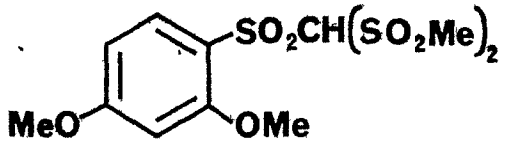


54

Reaction with 1,3-dimethoxybenzene.

The reaction of excess sulphene with 1,3-dimethoxybenzene was much more successful. A yield of 87% of the 3:1 adduct, **55**, was realised using similar



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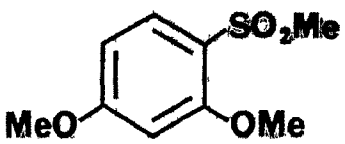
conditions to those used in the preparation of **48**. Reaction times were typically two hours, and quenching of the reaction after thirty minutes gave a much reduced yield. This early quenching also yielded about 3% of a 1:1 adduct with structure **56**. The two products were



56

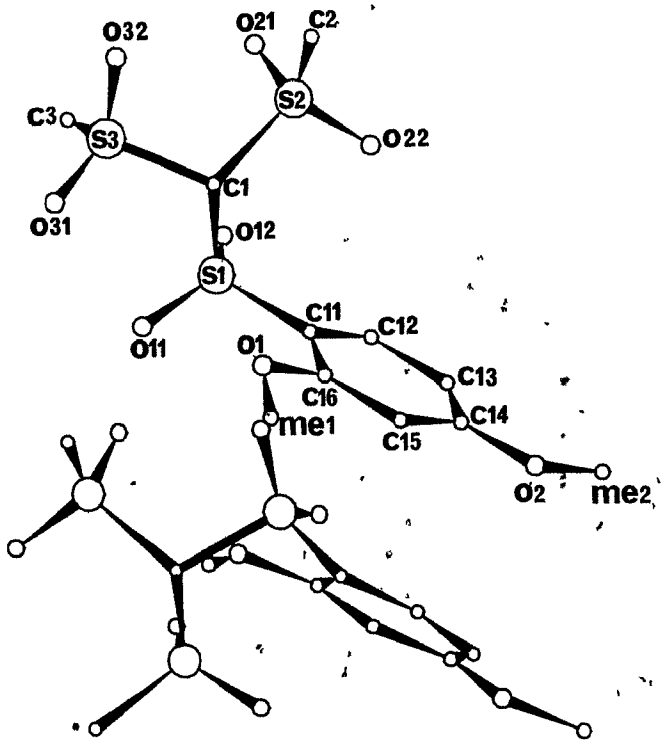
readily separable since **56** is sparingly soluble in base whilst **55** is readily soluble. The 1:1 adduct has been prepared previously by Gilbert[74] in 50% yield by the reaction of methanesulphonic anhydride with 1,3-dimethoxybenzene and the melting point obtained in the

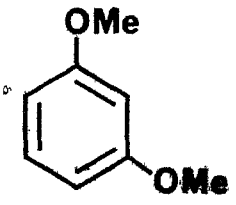
present study (101-2°C) compares well with that reported (103-5°C). The carbon-13 nmr spectrum which was previously unreported is also consistent with structure **56**. Spectra obtained for the 3:1 adduct, **55**, are also consistent with the structure given however, in order to establish this new reaction of sulphene firmly, the structure was also determined by X-ray diffraction. This study was completed without having to resort to a salt as for the 2,6-dimethoxypyridine adduct. Figure II presents a projection of the structure obtained for the unit cell and all the X-ray diffraction data are recorded in the Experimental section and in Appendix II of this thesis.

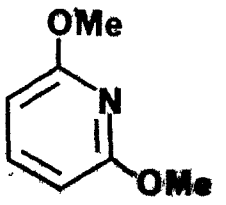
Attempts to obtain products from the reaction of sulphene with bromobenzene, chlorobenzene, naphthalene and 2,6-dimethylpyridine all failed. The result for the 2,6-lutidine is in concordance with the results of Grossert.[20]

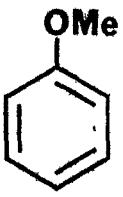
From the ease of reaction between sulphene and the aromatic substrates so far reported, and the accepted order of substituent activation in electrophilic aromatic substitution, an order of reactivity can be obtained (see below). At first sight 2,6-dimethoxypyridine seems to be too reactive since it is well known that pyridine rings are highly deactivated towards electrophilic aromatic substitution and that

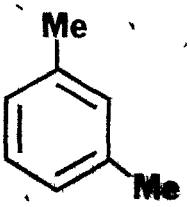
Figure II: Structure of bis(methylsulphonyl)-4-(1,3-dimethoxyphenyl)sulphonylmethane, 55.



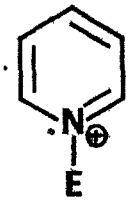








anisole is highly activated. For example, pyridine is 10^{-12} times as reactive as benzene for nitration with nitric acid whilst anisole is 10^{5} times more reactive than benzene.[75,76] This much decreased reactivity for pyridines is due to complexation of the electrophilic species present in solution with the nitrogen atom in the ring forming a species with structure 57. With



57

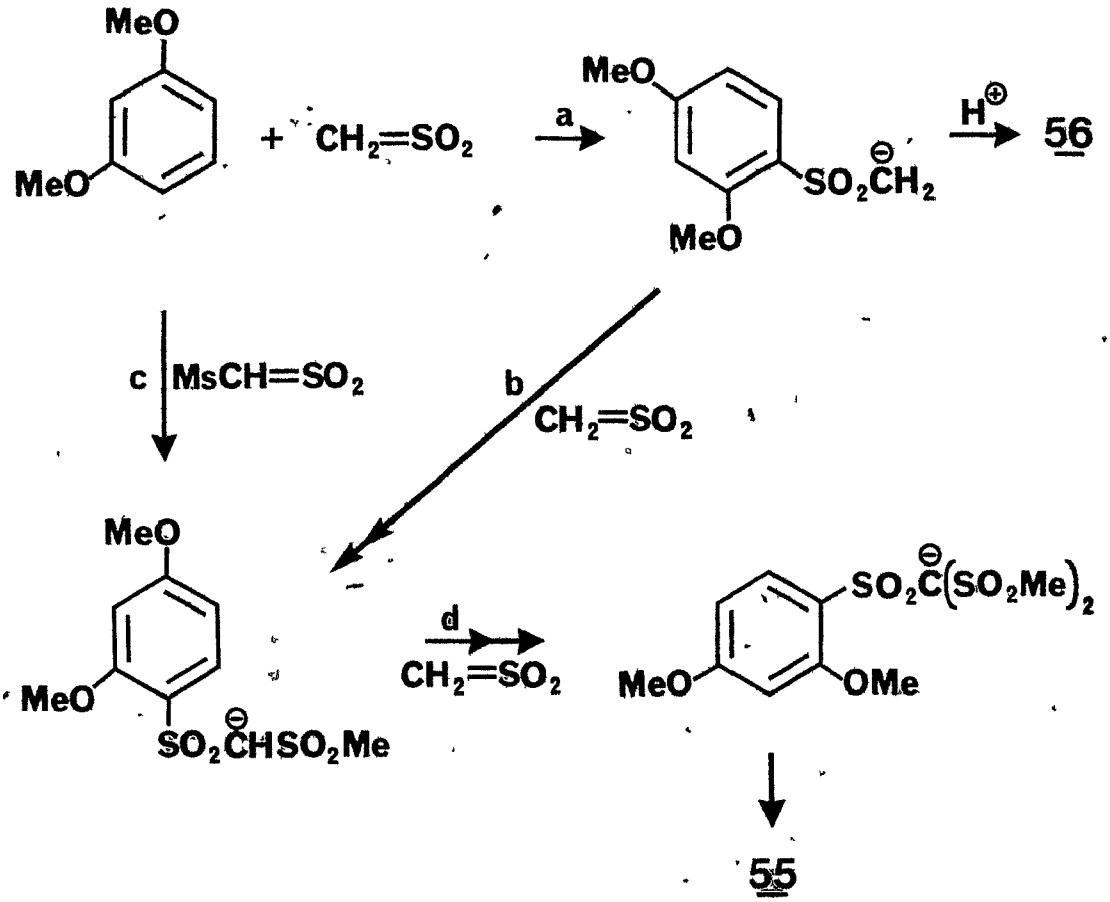
electrophiles larger than a proton it seems reasonable to assume that 2- and 6-substituted pyridines would tend to complex electrophiles less than other pyridine rings due to steric hindrance and hence the deactivation due to the quaternized nitrogen cation would be less likely. Although such an effect is rarely observed for a single substituent, 2,6-disubstituted pyridines are known to be much less able to coordinate electrophiles.[77,78] This effect has been referred to by some workers as the 'ortho effect'.[78,79,80,81]

In the case of 2,6-dimethoxypyridine the combination of two meta-substituted methoxyl groups which are highly activating and the concomitant 2,6-disubstitution of the pyridine ring by these two groups effectively enhances the reactivity of the ring towards electrophilic aromatic substitution compared with benzene and even anisole. However, the ring would be expected to be somewhat less activated than 1,3-dimethoxybenzene due to the electron-withdrawing nitrogen. The isolation of the 1:1 adduct **56** from this reaction and the fact that no 2:1 adduct has been formed suggests that the initial reaction of the aromatic substrate is with monomeric sulphene or sulphene complexed with the amine.

A suggested mechanism for the formation of **55** and **56** is presented in Scheme I, which could also apply to the formation of **48** with a different aromatic substrate.

The reaction of 1,3-dimethoxybenzene with a sulphene monomer, either complexed with triethylamine or not, produces a 1:1 adduct (step a) which on protonation would give **56**. The 1:1 adduct may react further with monomeric sulphene to form a 2:1 adduct (step b) which would rapidly equilibrate to give the more stable carbanion shown. This adduct may also be formed by the direct reaction of dimeric sulphene with the aromatic substrate (step c). Further reaction with monomeric

Scheme I:


MeO
MeO
+ CH2=SO2
a
MeO
SO2CH2
MeO
H⊕
56
c
MsCH=SO2
b
CH2=SO2
MeO
MeO
SO2CHSO2Me
d
CH2=SO2
SO2C(SO2Me)2
MeO
OMe
55

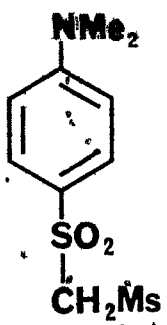
sulphene (step d) would then give 55 on work-up. Grossert and Bharadwaj[18] has shown that with no nucleophiles added sulphene is involved in a series of equilibria. With the addition of a relatively weak nucleophile, such as 1,3-dimethoxybenzene, the reactions are more complex as is shown in the scheme.

In the reaction carried out over two hours where the 3:1 adduct was isolated, all of the initially formed 1:1 adduct is obviously consumed. With a short reaction time some of this adduct remains and is protonated on work-up. It should be noted that initial attack by a sulphene species on 1,3-dimethoxybenzene will give a non-aromatic intermediate, this has not been shown in the scheme since rearomatisation would be a facile reaction and would be assisted by any of the several bases present in solution.

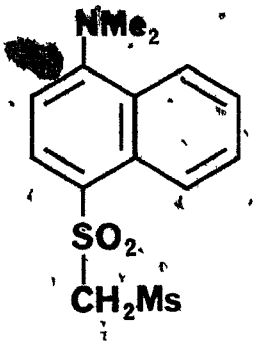
Reaction with dimethylamino-substituted aromatics

One of the most activating substituents for electrophilic aromatic substitution is the dimethylamino group. Bell and Ramsden[82] and Robertson et al.[83] have shown that N,N-dimethylaniline is 5 x 10^{18} times more reactive than benzene towards halogenation reactions. Such a difference in rates implies diffusion control for most reactions. Four aromatic compounds with this substituent were readily available for the present study, these were N,N-dimethylaniline, N,N-dimethyl-1-

naphthylamine, N,N-dimethyl-m-toluidine and N,N-dimethyl-p-toluidine. On reaction with sulphene the major products (>80% yield) were found to be 2:1 adducts **58**, **59** and **60** for the first three amines respectively whilst the last amine did not form an isolable product.



58



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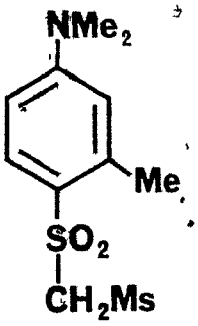
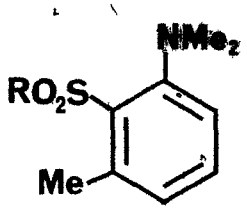


60

There was little conclusive evidence for the formation of a 1:1 adduct and a 3:1 adduct has never been observed. Proton nmr readily indicated the structures of **58** and **59** since the former exhibits an AA'BB' pattern whilst the latter shows an AB pattern as part of its aromatic region. Proton resonances are also present for the rest of the structure and other spectral techniques were used to confirm these structures. A CHNS analysis of **58** was obtained and this was consistent with an empirical formula of $C_{10}H_{15}NO_4S_2$ as expected.

The structure of methylsulphonyl-4-(N,N,3-trimethylanilino)sulphonylmethane, **60**, was more difficult

to establish as the structures of the three substituents were readily apparent but the substitution pattern was not. From a knowledge of the directive effects of the dimethylamino and methyl groups it can be assumed that there are only three possible structures for the product, viz. **61**, **62** and **63** where R = $CH_2SO_2CH_3$. Since



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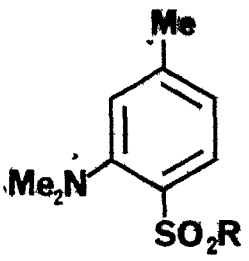

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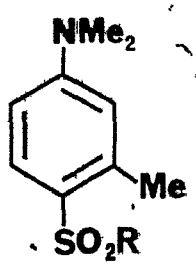
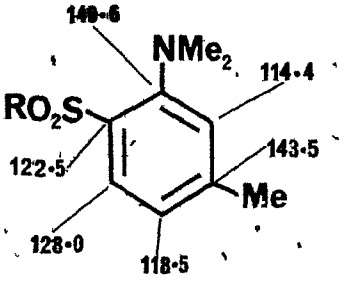


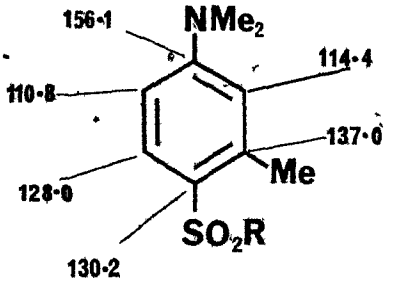
63

both initial substituents are ortho and para directing, substitution in the 5-position seems highly unlikely. Structure **61** does not fit the coupling observed in the aromatic region of the proton nmr spectrum and no product with the dimethylamino group ortho to the sulphene residue has been isolated. Simulated proton nmr spectra of **62** and **63** were similar to one another and to the actual spectrum obtained. Carbon-13 nmr shifts for the aromatic carbon atoms in each of the two structures were calculated using available data[84,85,86] and the results are shown in Figure III. Structure **63** fits the observed data much better than **62** and **63** is the expected

Figure III: Calculated carbon-13 chemical shifts for 62 and 63



62



63

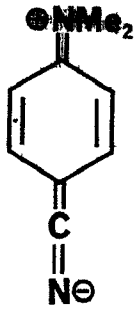
Experimental data: 108.51 (d), 114.06 (d),
130.77 (s), 133.14 (d),
139.68 (s), 153.93 (s).

isomer since steric hindrance would be much greater with the dimethylamino and sulphene residues ortho to one another. Furthermore, no useful product was obtained from N,N-dimethyl-p-toluidine and sulphene, which suggests that reaction ortho to the Me_2N group is not possible. The uv spectrum of **63** is very similar to that of the N,N-dimethylaniline adduct, **58** and this adds weight in favour of structure **63** over **62**. If the dimethylamino and sulphene residues were ortho a shift to shorter wavelength of some 65nm would be expected.[87]

The ultra-violet spectra of the three compounds **58**, **59** and **60** are interesting since compounds such as these with an electron-donating group para to an electron-withdrawing group exhibit very intense absorption at relatively high wavelengths. In general, this is due to a significant contribution of a dipolar structure to the overall structure of the molecule produced by 'through conjugation'. Such arguments have been advanced to explain rotational energy barrier [88] and dipole measurements [89] and have been confirmed by X-ray diffraction measurements [90,91] which indicate the expected bond lengths for such a system. For example, for p-cyano-N,N-dimethylaniline, structure **64** is an important contributor to the actual structure of the molecule. Such structural types are not nearly so important for the ortho substituted molecules with

similar substituents.

It is a matter of continuing discussion as to



64

whether a sulphone group can directly interact by delocalisation in this way by the use of d-orbitals on the sulphur atom. However a sulphone group is powerfully electron-withdrawing and it is well known that such a group is able to stabilise an adjacent negative charge effectively. So sulphones with structures like **58**, **59** and **60** should exhibit similar ultra-violet spectra, perhaps with λ_{max} shifted slightly to shorter wavelengths, compared with compounds containing group such as cyano. This is indeed the case and the results obtained in the present study complement and compare well with the results of Kumler[92] who established an order of electron-withdrawing ability based on the observed λ_{max} values in the ultra-violet spectra of a series of substituted N,N-dimethylanilines.

$-NO_2$ $-CHO$ $-COCH_3$ $-COOH$ $-SO_2NH_2$

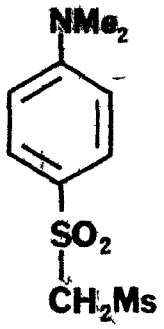
decreasing electron-withdrawing ability

From our results for compounds **58** and **60** we can place the sulphene residue between the acid and sulphonamide groups. The molar extinction coefficients observed in the present study ($\sim 2 \times 10^4$) are of similar magnitude to those obtained by Kumler ($1.9-2.9 \times 10^4$).

All of the dimethylamino-substituted aromatic compounds produced highly coloured solutions which developed as the reaction with sulphene progressed. The colours were generally green although some solutions looked red-brown. It was thus decided to analyse the reaction involving N,N-dimethylaniline in detail.

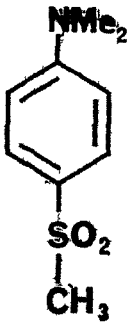
Separation of the reaction products was carried out using a vacuum-assisted chromatographic technique as described in the Experimental section. Depending on the ratio of sulphene to N,N-dimethylaniline five fractions were obtained in different amounts. In each separation a green-coloured component was isolated in extremely low yield (1%); such residues have often been observed during electrophilic aromatic susbstitution reactions of N,N-dimethylaniline and have usually been attributed to the formation of crystal violet-type dyes.[93,94,95]

Indeed the coloured residue obtained in this study shows similar proton nmr and ultra-violet spectra to those obtained for crystal violet, however, it was not possible to solve the structures of the compounds in this complex mixture. Table II details the isolated amounts of each of the other four fractions obtained in the separation. Fraction A was always the major product and is the 2:1 adduct already described with structure 58. Fraction B was always in very low yield and its



58

melting point agreed with that reported for p-methylsulphonyl-N,N-dimethylaniline, 65.[96] The formation of

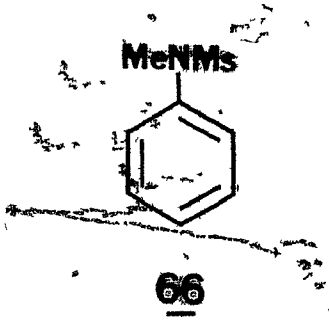


65

Table II: Results of the study of the reaction of N,N-dimethylaniline with sulphene.

DMA: sulphene molar ratio	yield of fractions A	B	C	D
2:1	43	-	9	8
1:1	50	-	5	5
1:2.5	72	1	8	5
1:6	85	1	8	-

this compound is consistent with the postulated pathway for addition of sulphene to aromatic compounds, as shown in Scheme I. The spectroscopic properties of fraction C were consistent with the sulphonamide, 66 and the



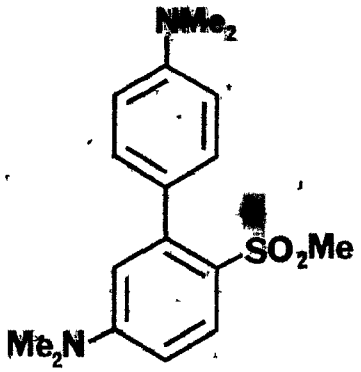
66

structure was confirmed by a mixed melting point with an authentic sample, prepared by the reaction of the mono anion of N-methylaniline with methanesulphonyl chloride.

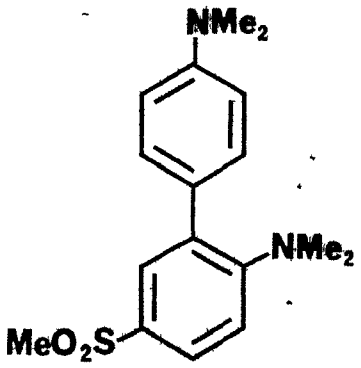
The structure determination of fraction D was much more complex. The proton nmr of this fraction indicated two different types of dimethylamino group and a methylsulphonyl group in the ratio of 2:2:1. The only other protons were in a complex aromatic multiplet, (ratio of aromatic to aliphatic protons ca 1:2). The mass spectrum required that the molecule contains two dimethylaniline rings. The infra-red spectrum indicated both aliphatic and aromatic C-H groups, the usual strong bands for a sulphone and a band at 1605 cm^{-1} due to aromatic C-C stretching. The carbon-13 nmr spectrum also indicated the presence of two different dimethylamino groups and two aromatic resonances, each being due

to two carbon atoms. A closer inspection of the aromatic region of the proton nmr spectrum of fraction D at 360 MHz revealed that there are two distinct systems: a AA'BB' pattern and a ABX pattern. This part spectrum is given as Figure IV. The CHNS analysis was consistent with an empirical formula of $C_{17}H_{22}N_2O_2S$.

From the foregoing information and chemical intuition there are two structures which reasonably explain these data, viz. **67** and **68**. Simulated spectra for the ABX part



67

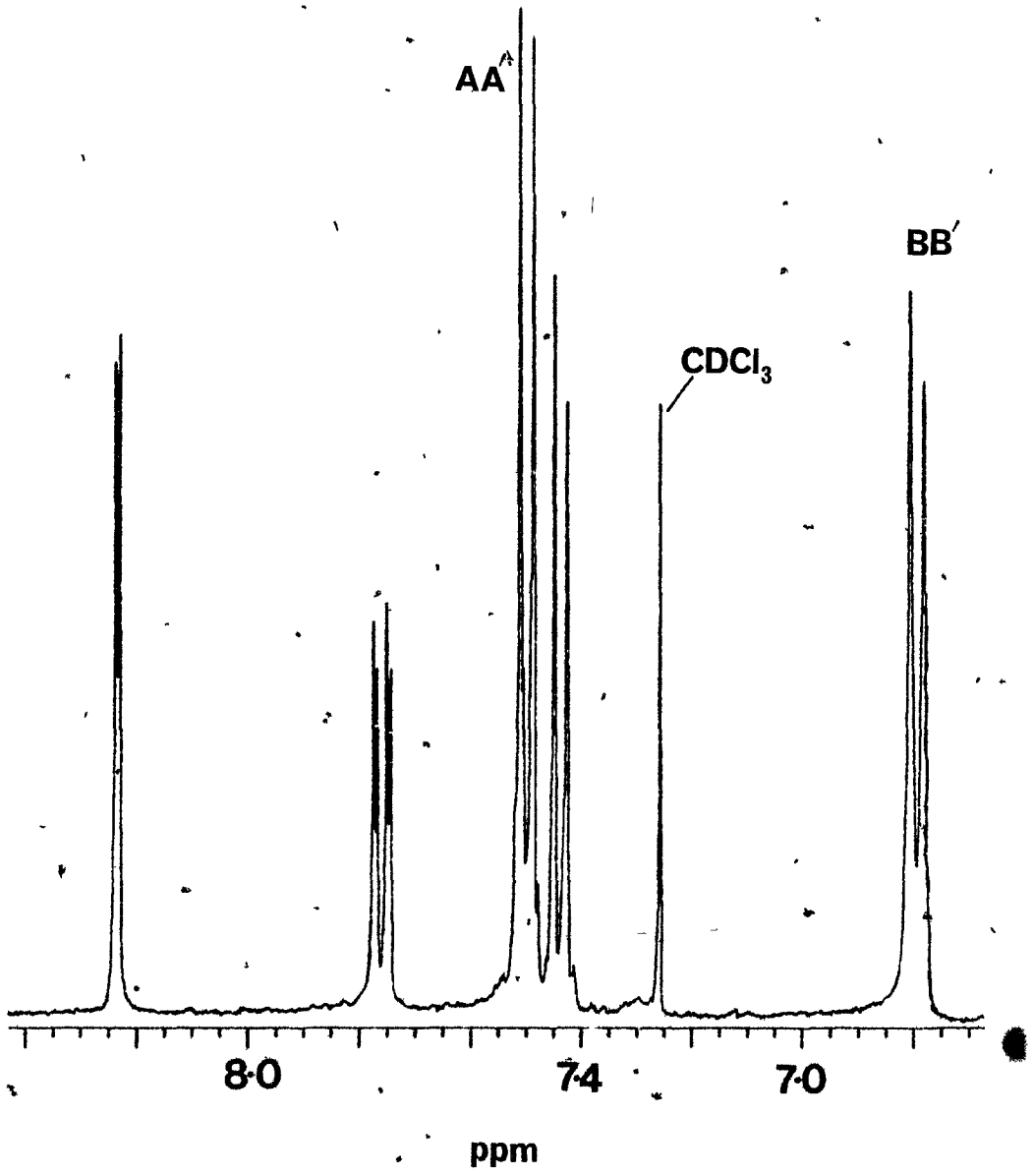


68

of the spectrum of these two structures were obtained using standard coupling constants and chemical shift data.[84,85,86] Although the position of the lines are not precisely reproduced, the splitting patterns are consistent only with biphenyl **68**.

The carbon-13 nmr spectrum of this compound also indicates that **68** is the structure of the biphenyl. Calculations of the carbon-13 chemical shifts for the

Figure IV: The aromatic region of the proton nmr spectrum of fraction D at 360 MHz.



tri-substituted rings in structures **67** and **68** were carried out using standard chemical shift data[84,85,86] and these are presented in Figure V. Since the data for the p-dimethylaminophenyl substituent are not available, data for phenyl were used instead. The observed chemical shifts of the biphenyl product in the aromatic region are 112.67 (d,2C); 123.84 (d); 126.74 (d); 127.1 (s); 127.58 (d,2C); 131.70 (d); 136.98 (s); 138.51 (s); 150.29 (s) and 151.50 (s). Of these the resonances at 112.67, 127.58 and one of each of the pairs 150.29 and 151.50 and 136.98 and 138.51 are typical of a *para* substituted compound with dimethylamino and aromatic substituents. Thus the resonances left are:

123.84

126.74

127.10 (s)

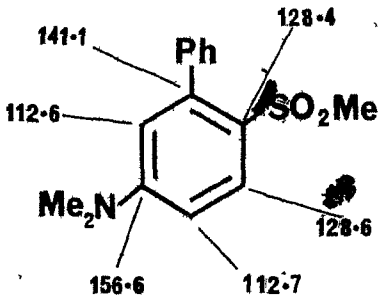
131.70

136.98 or 138.51 (s)

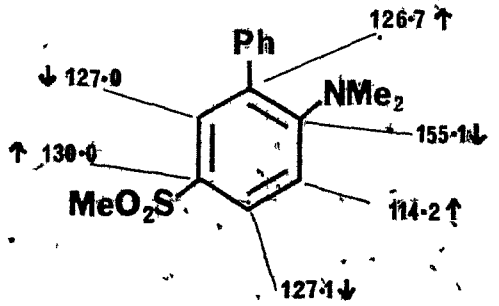
150.29 or 151.50 (s)

At first glance neither structure **67** nor **68** fits these data. In **68** however, there is a large group *ortho* to the dimethylamino group which will tend to twist it out of coplanarity with the attached phenyl ring. The effects of such twisting will reduce the importance of canonical forms like **64** to the overall structure and may have a profound effect on the electron density especially on

Figure V: Calculated carbon-13 chemical shifts for model compounds to simulate 67 and 68.



67



68

the carbon atoms attached directly to the nitrogen atom and those ortho and para to this group. Such electron density changes will affect the carbon-13 chemical shifts and will tend to increase the calculated values in Figure V as indicated with (↑) and decrease other values likewise (↓). These changes would make the calculated data for **68** fit the observed data more closely whilst no such fit can be obtained with **67**.

The ultra-violet spectrum of compound **68** is of some interest since, as has been mentioned above, there is the possibility of a sterically induced twist of the phenyl rings relative to one another in addition to the twisting of the dimethylamino group in the 2-position. Both of these kinds of steric effects have been studied using ultra-violet spectrophotometry[97] and one or both must surely occur in this compound.

Biphenyl itself exhibits a λ_{max} of 246nm and dimethylamino and alkylsulphonyl groups para to one another have a combined shift of 90nm to longer wavelength (data from this study) whilst an extra dimethylamino group will have a shift of 20nm to longer wavelength.[87] Thus the expected λ_{max} for **68** is 356nm whilst the observed λ_{max} is 308nm i.e. a shift to shorter wavelength is observed. In order for dipolar-like structures, such as that shown in structure **64**, to be important contributors to the overall structure of

the molecule the methyl groups in the dimethylamino moiety must be nearly coplanar with the aromatic ring. Such coplanarity is however, prevented by the steric effect of a large ortho group, the other benzene ring in this case.

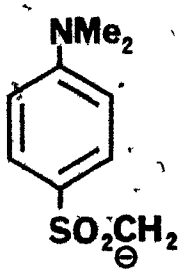
This twisting will tend to reduce the conjugation of the nitrogen lone pair with the ring and will thus lengthen the C-N bond and alter the electron density within the dimethylamino group. The electron density will be increased about the nitrogen atom and by the 'alternation effect' decreased around the two carbon atoms and increased around the six protons. The increased electron density around the protons is also evident in the abnormal position (upfield shift) of one of the dimethylamino groups in the proton nmr spectrum (at 2.80ppm cf. 3.05ppm in compounds **58** and **60**). The decreased electron density around the carbon atoms explains the downfield shift of one of the dimethylamino groups in the carbon-13 nmr spectrum (at 42.6ppm cf. ca. 40ppm in **58** and **60**).

The above discussion thus proves that the structure of the produced biphenyl is **68**, a structure containing a relatively rare substitution pattern.

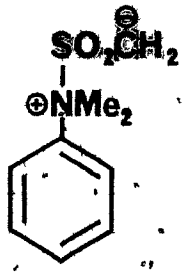
As can be seen from the details above, no 3:1 adducts were formed on reaction of sulphene with aromatic compounds containing dimethylamino

substituents. Thus Scheme I does not fully explain the reaction sequence involved. In this case there must be another reaction pathway with comparable energetics by which sulphene can be consumed. One possibility for such a pathway is that the nitrogen atom in these aromatic compounds can coordinate electrophiles. Such coordination is well known for N,N-dimethylaniline in other systems and has been invoked to explain the drastic reduction in reaction rates for some electrophilic substitution reactions.[98] The isolation of N-methyl-N-methylsulphonylaniline, **66** is taken as evidence in support of this complexation of sulphene by the nitrogen atom and similar products have been reported from several investigations of the reaction of N,N-dimethylaniline with aromatic sulphonyl chlorides.[99]

Both electrophilic aromatic substitution and complexation by the nitrogen of sulphene will lead to formal carbanions, **69** and **70** respectively which can both



69



70

coordinate more sulphene units. Unless N-demethylation of **70** occurs to form **66**, the sulphene units coordinated to the nitrogen atom will be hydrolysed off on work-up of the reaction mixture.

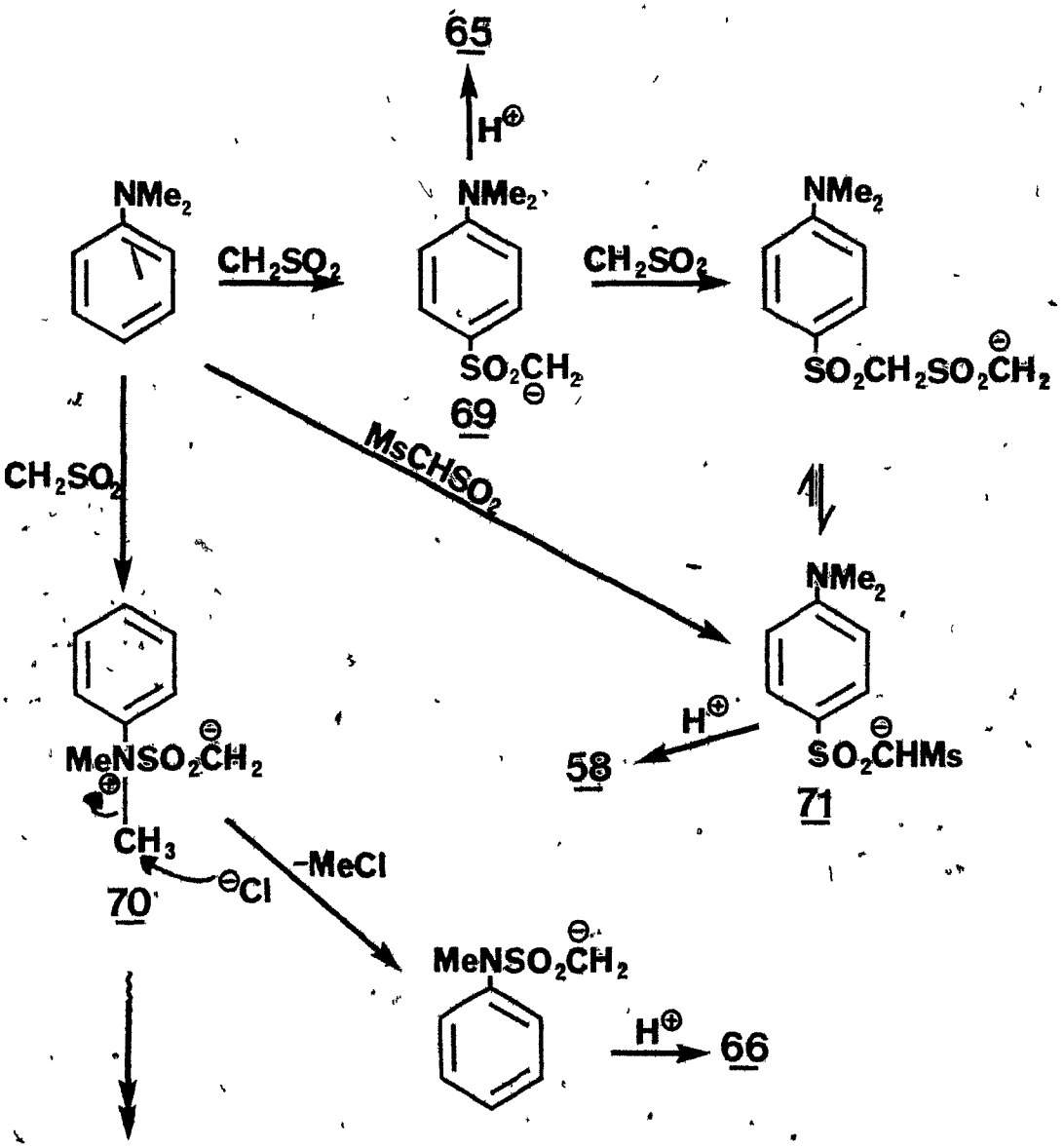
A suggested mechanism for the formation of **58**, **65** and **66** is presented in Scheme II. Species such as **69** and **71** which have an $-SO_2R$ group *para* to the dimethylamino group would not be expected to coordinate sulphene at the nitrogen atom since the electron density at this atom is significantly reduced by 'through conjugation' as described earlier. Species **71** may be formed either by step-wise addition of two sulphene units or by reaction with a dimeric sulphene species in one step. No 3:1 adduct has ever been isolated for such compounds and so **71** does not react further with sulphene. The other carbanions and other nucleophiles present in the reaction mixture must be more reactive than this species and hence only a 2:1 adduct is formed.

The reaction mixture in these reactions must contain a complex series of equilibria all competing with each other. The formation of the biphenyl **68** is discussed in detail in a subsequent section.

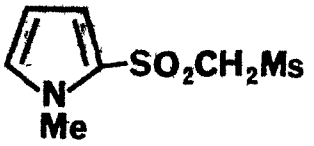
Reaction with pyrroles

The reactions of sulphene with pyrrole and N-methylpyrrole were also attempted. With pyrrole itself,

Scheme II:


65
H⊕
NMe2
CH2SO2
NMe2
CH2SO2
NMe2
SO2CH2⊖
69
SO2CH2SO2CH2⊖
CH2SO2
MsCHSO2
NMe2
MeNSO2CH2⊖
CH3
⊖Cl
70
-MeCl
H⊕
58
SO2CHMs⊖
71
MeNSO2CH2⊖
H⊕
66

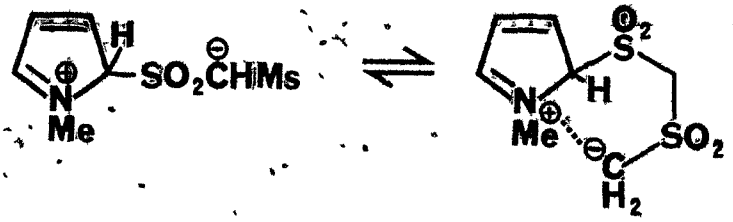
the result was a reddish-brown tarry mass whilst N-methylpyrrole gave a 2:1 adduct, **72**. Pyrroles are highly



72

activated towards electrophilic aromatic substitution and the reaction with sulphene was not surprising. Pyrrole is very prone to polymerisation under conditions where electrophiles are present.[100]

For pyrroles, 2-substitution is generally the preferred mode of reaction and this can be explained qualitatively by the fact that there are three possible resonance forms for the intermediate formed by 2-substitution compared with only two on 3-substitution. Neither a 1:1 or a 3:1 adduct were isolated in this reaction which is perhaps surprising. Obviously the anion **73** does not react further with sulphene; perhaps this



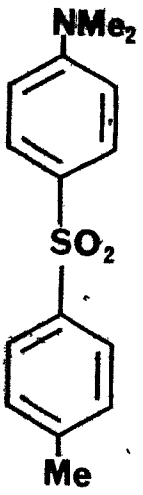
73 **74**

dipolar species is stabilised by the formation of a rather tight ion-pair and equilibration to **74** would form an ion-pair which is also a six-membered ring. Such species are generally favourable and work-up of this equilibrium mixture would produce the product **72**.

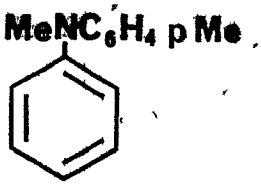
An alternative route to the biphenyl derivative **68** and similar species

Since p-methylsulphonyl-N,N-dimethylaniline, **65**, had been prepared in low yield as described above, its synthesis by an alternative route was attempted. Dondoni and Tadisco[96] had previously prepared the compound by a circuituous route, also in low yield. It therefore was attractive to attempt a new simple synthesis using a Friedel-Crafts type reaction. Vriesen[101] and Truce and Vriesen[102] have reported the sulphonylation of aromatic compounds using methanesulphonyl chloride and a Friedel-Crafts catalyst. These workers found that the introduction of a methylsulphonyl group into an aromatic ring was only successful for benzene or other aromatic compounds of similar reactivity such as toluene and chlorobenzene. Results for the more reactive aromatic compounds were not reported save for anisole which gave the sulphonate. Many reports in the early 1900's concerned the reaction of N,N-dimethylaniline with aromatic sulphonyl chlorides to form colourful dyes and Gebauer-Fülnegg and Schwarz[99] have shown that depending

on the reaction conditions, reaction of N,N-dimethylaniline with tosyl chloride gives both substitution, 75, and N-demethylation, 76.



75



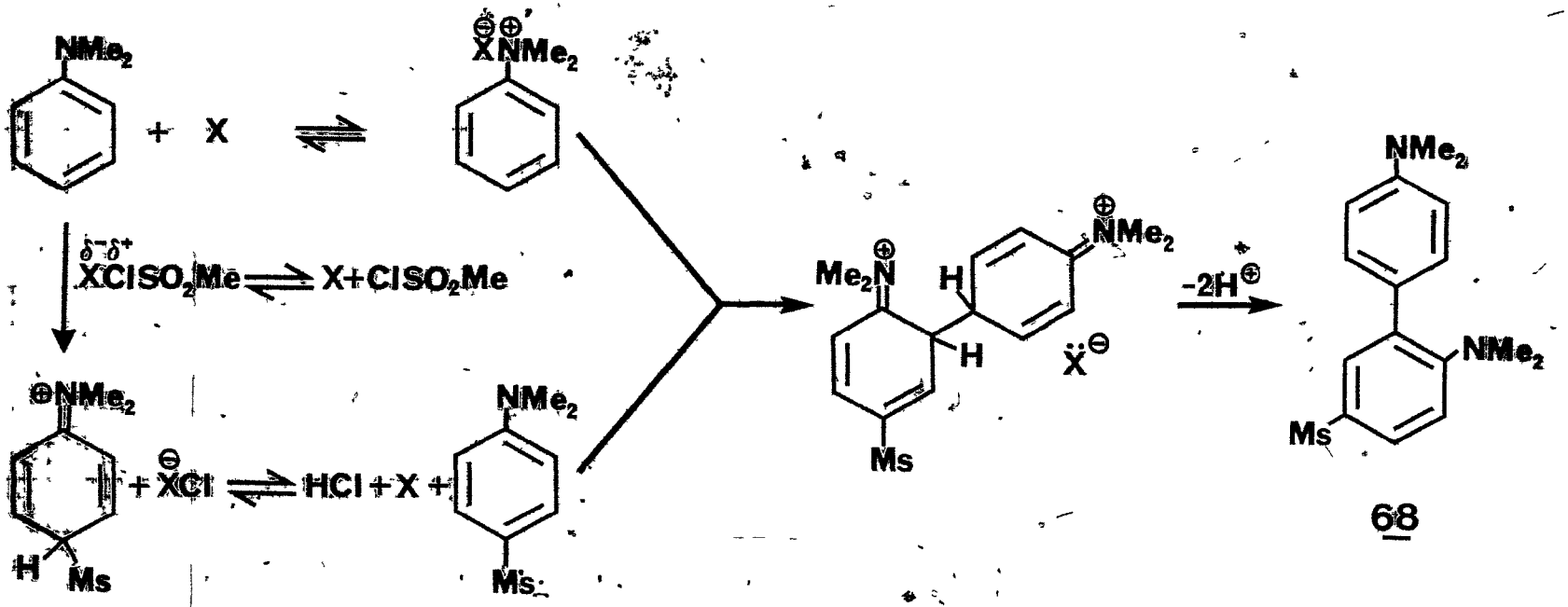
76

The fact that 75 could be prepared in a reasonable yield gave hope that 65 could be synthesised in a similar fashion by the reaction of methanesulphonyl chloride with N,N-dimethylaniline. The synthesis was unsuccessful when aluminium trichloride was used as a catalyst. However, if antimony pentachloride was used, a deep-red coloured reaction mixture was formed and although 65 was not formed, a 21% yield of 68 was realised. This yield could be increased to 41% by use of an excess of the catalyst. Compound 68 was identified as such since it showed identical spectral properties to the product obtained previously and a mixed melting

point with the authentic sample was undepressed. It thus seems likely that **68** was formed in the sulphene reaction by direct attack of the aromatic compound on methanesulphonyl chloride and that sulphene is not an intermediate in this process since no dimeric sulphene residue on a biphenyl was isolated. Further support for this point is that the yield of **68** was much reduced (<1%) if the methanesulphonyl chloride was added to a mixture of triethylamine and N,N-dimethylaniline to form sulphene. A possible mechanism for the formation of **68** is given in Scheme III. In order for such a scheme to work several conditions must be met. The electrophile (X) must interact with both the methanesulphonyl chloride and the dimethylamino group to form complexes of reasonable stability. It must also have a relatively low reduction potential; *i.e.* it should be able to accept a pair of electrons readily. Of course, two different species may be present each filling one of these roles. Antimony pentachloride meets both of these conditions, it is known to be a good Friedel-Crafts catalyst[103] and it is able to accept electrons by reduction of antimony (V) to antimony (III). When either antimony trichloride or aluminium trichloride were used as catalysts no reaction occurred. Although both have been used as Friedel-Crafts catalysts,[103] neither is easily reduced.

Formation of **68** is *via* a complex series of

Scheme III:

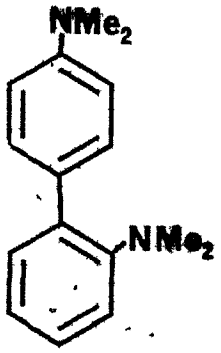

NMe2
+ X
XNMe2
δ⁻δ⁺
XClSO2Me
X+ClSO2Me
⊕NMe2
+ ⊖XCl
HCl+X+
NMe2
H
Ms
Ms
65
Me2N
H
H
Ms
NMe2
-2H⊕
NMe2
NMe2
Ms
68

equilibria whence some dimethylamino groups can be uncoordinated in the presence of an electrophile like antimony pentachloride. If the formation of **65** occurs as shown then it is reasonable to assume that the dimethylamino group in this compound will not be coordinated owing to the 'through-conjugation' effect described earlier.

The highly coloured reaction mixture suggests that radical ions may also be involved in the reaction mechanism. Such involvement has been postulated and proved in some examples of Friedel-Crafts reactions.[104] Unfortunately due to the heterogeneous nature of the reaction mixture amongst other things, an esr study was not possible in the present work.

The formation of the biphenyl **68** constitutes a unique reaction and an attempt was made to produce other biphenyls by similar processes. Such reactions would be useful since synthetic routes to unsymmetrical biphenyls are usually long and result in low yields. The reaction of N,N-dimethylaniline with antimony pentachloride in the presence of methyl iodide, sulphuryl chloride, bromine and acetyl chloride yielded no isolable products. The reaction of N,N-dimethylaniline with antimony pentachloride with no added electrophiles yielded a complex mixture of products. Chromatographic separation was not altogether successful although a

yellow, oily solid with structure 77 was isolated. This

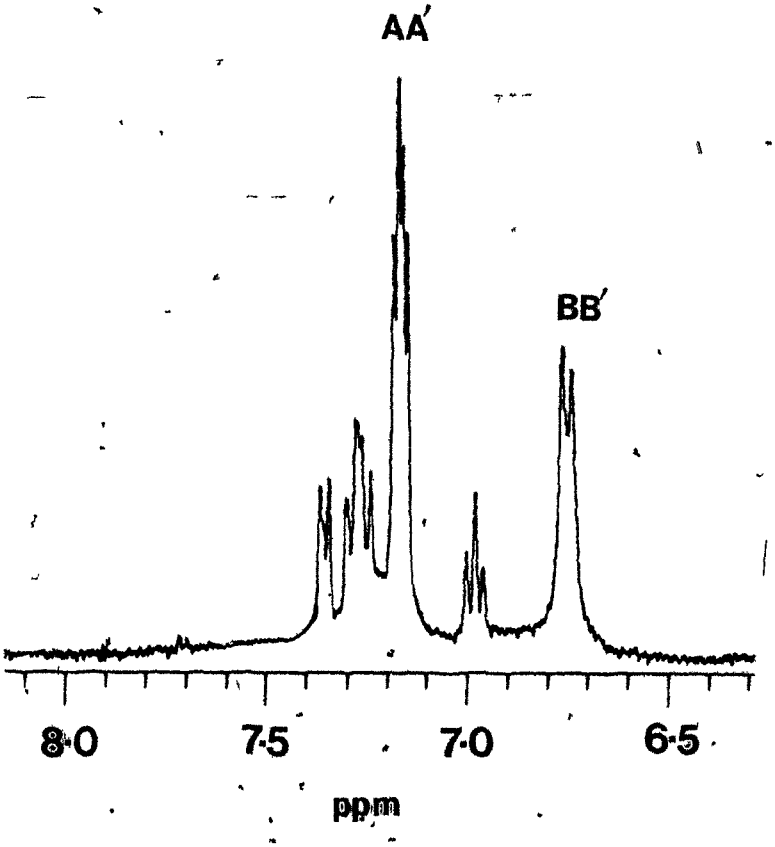


77

structure was confirmed by its proton nmr and mass spectra only since its yield was very low. The aromatic region of the 360 MHz proton nmr spectrum of 2,4'-bis(dimethylamino)biphenyl, 77, is presented in Figure VI and this is consistent with a ABCD pattern and a AA'BB' pattern overlapping, as expected for this structure. Although 4,4'-bis(dimethylamino)biphenyl was not isolated it was presumably formed also.

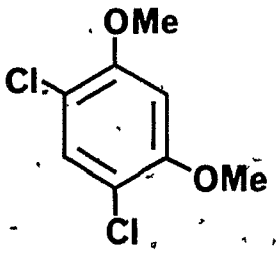
Other products formed in the reaction were isolated in very low yields and these were tentatively identified using a mass spectrum of the crude mixture. The peaks at 254, 272, 274, 306 and 308 Daltons were assigned to structures 78-82 respectively and are shown in Figure VII; their isotope peaks were consistent with the structures within experimental error (n.b. some of these overlapped). 2,4'-Bis(dimethylamino)-5-methyl-

Figure VI: The aromatic region of the proton nmr spectrum of 2,4'-bis(dimethylamino)-biphenyl, 77.



methylbiphenyl, **78**, was likely formed by reaction of N,N-dimethylaniline with methyl chloride formed by a N-demethylation reaction such as depicted in Scheme II. Compound **78** was also prepared as part of a complex impure mixture from the reaction of N,N-dimethylaniline and N,N-dimethyl-p-toluidine with antimony pentachloride (evidence from mass spectrum). Since antimony pentachloride is also a fairly powerful chlorinating agent, and has been used for many years as such,[105] several of the products contained chlorine; these atoms are located solely on the basis of the expected directing powers of the dimethylamino group. Compounds **79** and **81** are tricyclic and are probably formed via the coupling of radicals.

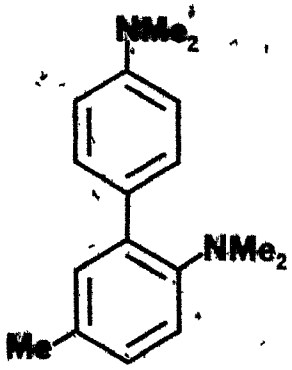
Reaction of 1,3-dimethoxybenzene with antimony pentachloride produced no biphenyl products. The simple dichlorinated compound **83** was produced in 55% yield. The



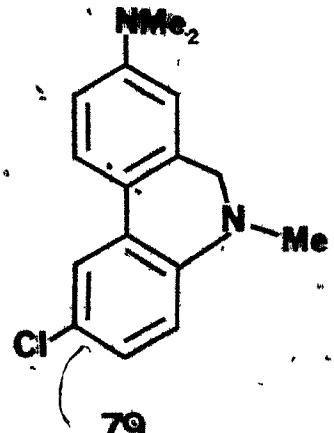
83

reaction mixture was again highly coloured suggesting the existence of radical ions but no coupling products

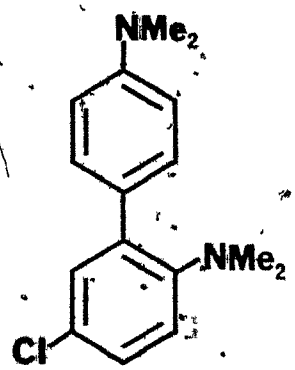
Figure VII: Compounds 78 - 82.



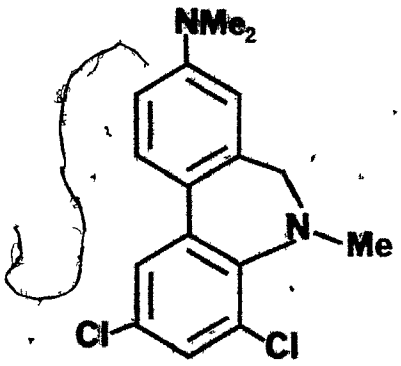
78



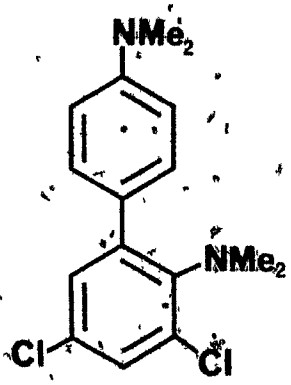
79



80



81



82

were observed in the mass spectrum indicating that such species are not important in this case. Compound **83** had been prepared previously;[106] the melting point and spectral data obtained in the present study agree well with the reported data and that expected. The fact that biphenyls were produced in the reactions involving dimethylamino substituted aromatic compounds is undoubtedly due to the great activation of this group.

Reactions of substituted sulphenes

A study of the literature indicates that substituted sulphenes have been little studied in comparison with sulphene itself (see for example the reviews of King[14] and Opitz[22]). Of these substituted species methylsulphene and phenylsulphene have been the most studied probably because the corresponding sulphonyl chlorides are relatively cheap and easily obtainable. However, both have problems associated with their chemistry.

Phenylsulphene has a propensity to decompose to form trans-stilbene by loss of sulphur dioxide although Hamid and Trippett[107] have shown that it undergoes cycloaddition reactions with enamines and ynamines. On the other hand methylsulphene reactions generally occur in lower yield than do equivalent reactions using sulphene. For example Opitz et al. have shown that the

cycloaddition reactions of methylsulphene with enamines[108] and ketene-N,N-acetals[109] proceed in yields of less than 10% whilst sulphene reacts to give products in 70% and 50% yields respectively.

In the present study the reactions of aromatic compounds activated towards electrophiles and methylsulphene and phenylsulphene were investigated and the results indicate similar problems to those outlined above.

Phenylsulphene reactions

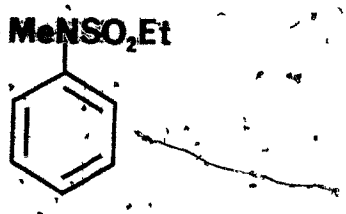
Attempts to obtain electrophilic aromatic substitution products from phenylsulphene with both N,N-dimethylaniline and 1,3-dimethoxybenzene both failed even though a variety of reaction conditions (temperature and solvent) were used. In all reactions the aromatic compound was recovered nearly quantitatively and trans-stilbene was the only product. King and Durst[110] have shown that decreasing the polarity of the solvent decreases the formation of the trans-stilbene however this had no observable effect in the present study.

It is concluded from these results that dimerisation of phenylsulphene forming the episulphone followed by a Ramberg-Bäcklund-type reaction to form trans-stilbene, as suggested by King and Harding[111] must be a much more

favourable route than electrophilic aromatic substitution.

Methylsulphene reactions

The reaction of methylsulphene, formed from the reaction of ethanesulphonyl chloride, with 1,3-dimethoxybenzene produced ethanesulphonic acid as the major product after work-up of the reaction; no adducts arising from electrophilic aromatic substitution were isolated. With the more activated N,N-dimethylaniline, an analysis of the dichloromethane-soluble products indicated that less than 5% of these contained a para-substituted aromatic ring although there were suggestions of such substitution. The major organically soluble product is **84**.



84

As has been discussed above, such a product is likely formed by coordination of the alkylsulphene followed by nucleophilic attack causing N-demethylation. This product was only obtained in 9% yield.

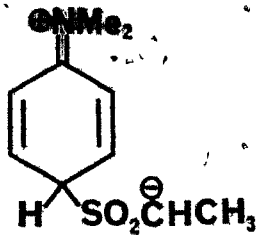
Various conditions were used in order to coax methylsulphene into an electrophilic aromatic substitution reaction but these all failed. King and Harding[111] have shown that the use of trimethylamine as the base in the formation of methylsulphene significantly increases the yield of β-sultones in reactions with electrophilic carbonyl compounds, however, the use of trimethylamine had no such effect here.

It is also interesting to note that no dimeric species of type **85** are apparently formed in the reaction

85

since they would produce readily identifiable sulphonic acids on work-up of the reaction.[18,19]

Since a methyl group is electron donating this will tend to stabilise a species which is overall electron deficient such as sulphene. However, this electron donation would also tend to destabilise the negative charge in the likely intermediate **86** for electrophilic aromatic substitution. These two effects would both



86

serve to increase the activation energy for such a reaction and here this is sufficient to direct the path of the reaction to the N-demethylation process. Of course, steric effects are likely also to inhibit reaction.

Reactions of azasulphenes

In this study the reactions of a few azasulphenes with N,N-dimethylaniline, 1,3-dimethoxybenzene and anisole have been investigated. Azasulphenes were usually generated in situ under dry conditions by the reaction of a sulphamoyl chloride with triethylamine in an inert solvent such as benzene or tetrahydrofuran at 10° to 20°C. Acetonitrile was not used as a solvent since it is known to form adducts with carboalkoxy-azasulphenes.[38] Reactions attempted at the lower temperatures used for the sulphene reactions (i.e. -30° to -20°C) yielded no useful products which would be in accordance with an anticipated lower reactivity of azasulphenes as compared to sulphene.

The carboalkoxysulphamoyl chlorides used to generate

the corresponding azasulphenes were prepared by the careful reaction of chlorosulphonyl isocyanate with the relevant hydroxyl-containing compound.[36,37] Preparation of ethylsulphamoyl chloride was attempted, using the method of Hansen,[112] by the reaction of ethylamine hydrochloride with a large excess of sulphuryl chloride. This reaction is reported to proceed in 42% yield on refluxing for eighteen hours; however, 20% was the best yield obtained in the present study, the major product being N,N'-diethylsulphamide, **87**. The method of Kloek and

$EtNHSO_2NHEt$

87

Leschinsky,[34] although a two-step preparation, produced ethylsulphamoyl chloride in 71% yield after distillation, with no sulphamide as side-product.

Anisole gave no useful products with either ethylazasulphene or carboethoxyazasulphene, **88**. The

$EtO_2CN{=}SO_2$

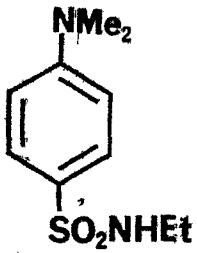
88

starting aromatic compound was recovered quantitatively together with an almost quantitative yield of

ethylsulphamic acid, the latter being formed by reaction with water on work-up of the reaction mixture.

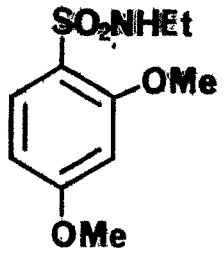
Reactions of ethylazasulphene .

N,N-Dimethylaniline reacted with ethylazasulphene to produce N,N-dimethyl-N'-ethylsulphanilamide, **89**, in 55%



89

yield after recrystallisation from methylene chloride-petroleum ether. This compound was also prepared similarly by Atkins and Burgess[47] who realised a 47.4% yield. The melting point and the infra-red and proton nmr spectra agreed well with those reported save that the aromatic region exhibited a AA'BB' pattern typical of a compound of structure **89** and not a multiplet as reported.[47] 1,3-Dimethoxybenzene also reacted with ethylazasulphene, in this case N-ethyl-2,4-dimethoxybenzenesulphonamide, **90**, was produced in 54% yield after recrystallisation. The proton nmr spectrum exhibited a ABX system expected for such a structure and



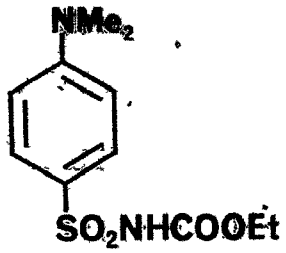
90

also included two different methoxyl signals at 3.92 and 3.99 ppm. The methylene group at 2.18 ppm showed a broadened quartet due to coupling with the adjacent NH group, this broadening was removed on shaking with D_2O. The carbon-13 nmr spectrum confirmed the structure of **90**; this spectrum also indicated two separate resonances for the methoxyl groups.

As was indicated above, Atkins and Burgess[47] have briefly mentioned the reaction of N,N-dimethylaniline with ethylazasulphene. The last paragraph of the discussion in their paper simply indicates that a reaction takes place without any comment on its significance. Unfortunately anisole does not react with ethylazasulphene and so it seems that only very highly activated aromatic compounds can be expected to react with this potent electrophile.

Reactions of carboalkoxyazasulphene

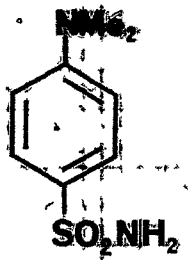
N,N-Dimethylaniline reacted with carboethoxyazasulphene, **88**, to produce N,N-dimethyl-N'-carboethoxysulphanilamide, **91**, in 61% yield (Atkins and



91

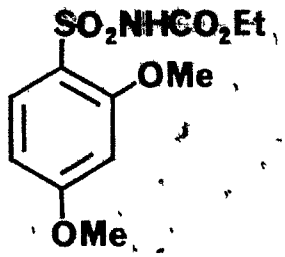
Burgess[47] reported 36%). The melting point and the infra-red and proton nmr spectra obtained in the present study compare well with those reported except that again a AA'BB' pattern was clearly evident in the aromatic region of the proton nmr rather than the reported multiplet. The carbon-13 nmr spectrum was also recorded and confirms the structure of the product.

N,N-dimethylsulphanilamide, **92**, may be prepared in



92

nearly quantitative yield by the hydrolysis of **91** in aqueous, acidic methanol. 1,3-Dimethoxybenzene also reacts with carboethoxyazasulphene to produce a similarly substituted product, **93**, which is readily hydrolysed to **94** in quantitative yield.



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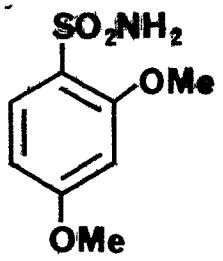
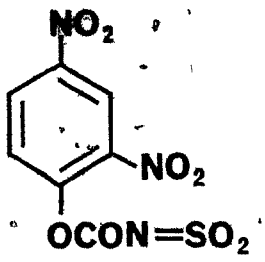


94

Thus a new synthesis of aromatic sulphonamides from highly activated aromatic compounds is presented. Such species have been prepared in earlier years by other routes in relatively low yields.[113]

Carbomethoxyazasulphene and carbophenoxyazasulphene also react with N,N-dimethylaniline and 1,3-dimethoxybenzene in a similar fashion. Carbo-(2,4-dinitro)phenoxyazasulphene, **95** on the other hand yields the sulphonamide directly on work-up, *i.e.* no separate hydrolysis is required. This latter reaction also occurs in much lower yield than with the other azasulphenes



95

which tends to suggest that 95 decomposes readily.

The fact that the electrophilic aromatic substitution reaction with azasulphenes requires a higher temperature than with sulphenes themselves indicates that the activation energy for the former reaction is higher than that for the latter.

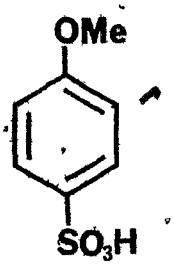
Reactions of sulphur trioxide

In this study the sulphur trioxide complexes with trimethylamine and with pyridine which were used, were those which are commercially available (Aldrich # 13,587-9 and S 755-6 respectively). As was discussed in the previous chapter, the pyridine complex is the more reactive of the two. Table III shows the yields of the sulphonic acids 96, 97 and 98 produced in the reaction of anisole, 1,3-dimethoxybenzene and N,N-dimethylaniline respectively with the sulphur trioxide complexes. It

Table III: Yields obtained in the aromatic sulphonation reactions.

Sulphur Trioxide Complex:	SO_3.py			SO_3.NMe_3		
Aromatic Compound:	50°	80°	120°	50°	80°	120° *
Anisole	0	0	trace	0	0	0
1,3-dimethoxy-benzene	0	8%	35%	0	trace	20%
N,N-dimethyl-aniline	0	20%	50%		0	35%

* Reaction temperature



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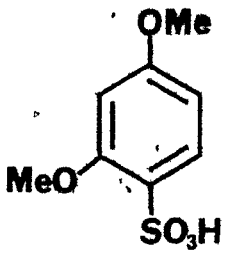

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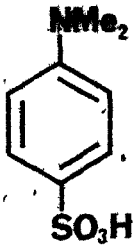


98

should be noted that each reaction carried out using a two-fold excess of the sulphur trioxide-complex in a sealed tube for six hours at the temperature stated. No reaction occured at room temperature for any of the aromatic compounds.

Anisole gives no useful yield of **96** under any of the conditions used here although a trace of such a product was indicated by a possible AA'BB' pattern in the proton nmr spectrum of the reaction with the sulphur trioxide-pyridine complex at 120°C, The reactions of the other two aromatic compounds with sulphur trioxide have not been reported earlier as far as the author is aware. However, neither of these compounds give good yields of their respective sulphonic acids. All spectral data obtained for the two products were in agreement with structures **97** and **98**.

From these results it can be inferred that the

activation energy for the reaction of the sulphur trioxide-trimethylamine adduct, which is the reaction most relevant to the sulphene and azasulphene reactions, is higher than for both of these other reactions.

The work described in this chapter has shown that the three species considered i.e. sulphenes, azasulphenes and sulphur trioxide are similar in their electrophilic aromatic substitution reactions. Such similarities extend to much of the other chemistry of these species as shown in Chapter 2. Although such similarities have been alluded to by several groups of workers, for example Williams and co-workers,[114,115] the author is unaware of any previous direct, detailed comparison of the species. It is hoped that the present work makes such a direct comparison and hence puts the chemistry of these species in a better perspective.

A new method for the introduction of an $-SO_2X$ group (where X is carbon or nitrogen) into aromatic compounds activated to electrophilic substitution has been presented and has been shown to be of some synthetic utility. The preparation of aromatic sulphonamides by the hydrolysis of the carboalkoxyazasulphene products occurs under rather mild conditions and such products are used in a wide variety of applications.[116]

Serendipity has provided a new, albeit low-yield synthesis of some novel substituted biphenyls.

Suggestions for further work

One-to-one adducts of sulphene with aromatic compounds may possibly be obtained by the use of different conditions to those employed here, for example, generation of sulphene in a medium where it is more reactive has been described,[117] perhaps use of this system will allow rapid reaction of aromatic compounds with a single sulphene unit; quenching of the reaction would thus produce 1:1 adducts.

Another interesting study would be the investigation of the cleavage of $C \rightarrow SO_2$ bonds in the 2:1 and 3:1 adducts obtained in the current work in order to investigate selective cleavage reactions. There are several methods for such cleavage reactions and these have been described elsewhere.[3]

Although Snyder has reported calculations of the structure and electron density of sulphene[15] no such data are available for azasulphenes whilst the structure of sulphur trioxide is well known. Such calculations for azasulphenes would be interesting and potentially useful since extensions of these results may provide more information about the relative reactivities of the three species with nucleophiles such as aromatic compunds.

PART II

CONCERNING THE SYNTHESIS AND PROPERTIES OF SOME β-KETOSULPHONES AND THEIR DERIVATIVES.

CHAPTER 4

INTRODUCTION - β-KETOSULPHONES

β-Ketosulphides, sulphoxides and sulphones.

β-Ketosulphides, **99**, sulphoxides, **100** and sulphones, **101**, all contain a methylene group which is

$RCOCH_2SR'$ — $RCOCH_2SOR'$ — $RCOCH_2SO_2R'$

99 **100** **101**

doubly activated owing to the electron-withdrawing properties of the carbonyl group and the sulphide, sulphoxide or sulphone moiety respectively. The electronic effects of these groups stabilise a carbanion formed on the central carbon atom and this allows several rather facile reactions, for example alkylation and halogenation, to occur in a similar manner to the typical reactions of 1,3-dicarbonyl compounds.[118] The stability of the monoanion species, **99**, **100** and **101** increases as the sulphur oxidation level increases whilst their reactivity increases in the converse order.

The facility of the reaction mentioned above gives β-ketosulphides, sulphoxides and sulphones potential as

synthetic intermediates[119] and this usefulness is increased by several methods that have been developed for the subsequent cleavage of the C-S bond.

Formation of β-ketosulphides is usually by the sulphenylation of ketones using a disulphide, sulphenyl halide or similar reagent,[120,121] for example:

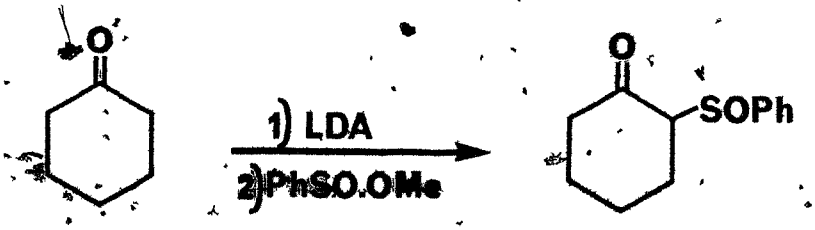
$$RSCH_2COR' + R''SSR'' \xrightarrow{B} RSCH(SR'')COR'$$

However, β-ketosulphoxides and sulphones are normally prepared either by the oxidation of the corresponding β-ketosulphide,[119,122] or more usually from the reaction of the anion of an alkylmethylsulphoxide or sulphone with an ester[123,124] thus:

$$RSO\overset{\ominus}{C}H_2 + R'CO_2R'' \longrightarrow R'COCH_2SOR$$

This reaction is generally only synthetically useful if the sulphoxide or sulphone is symmetrical and is normally carried out with dimethyl sulphoxide or sulphone. β-ketosulphoxides have also been prepared in fairly good yields (60-90%) by the reaction of an enolate anion with an ester of a sulphinic acid[125,126]

e.g.



Other methods for the preparation of these compounds have been reviewed elsewhere[119] and will not be discussed further here.

The reactions of β-ketosulphides and β-ketosulphones have not been investigated to the same depth as for those of β-ketosulphoxides. This is probably because β-ketosulphoxides are of intermediate reactivity between the other two species. Most studies of these species are concerned with the use of the sulphoxide, or other group, as a control element which is removed during a later step in the synthesis. Consequently the removal of such a group has been extensively studied and has resulted in two alternative routes to such removal:

$$RCOCR'R''SOR''' \xrightarrow{Al/Hg} RCOCHR'R''$$

$$RCOCR'R''SOR''' \xrightarrow{AcOH/Zn} RCOCHR'R''$$

Russell et al.[127,128] have been particularly active in the use of β-ketosulphoxides and have produced a wide-range of 1,2-dioxygenated compounds by various work-up procedures as detailed in Scheme IV.

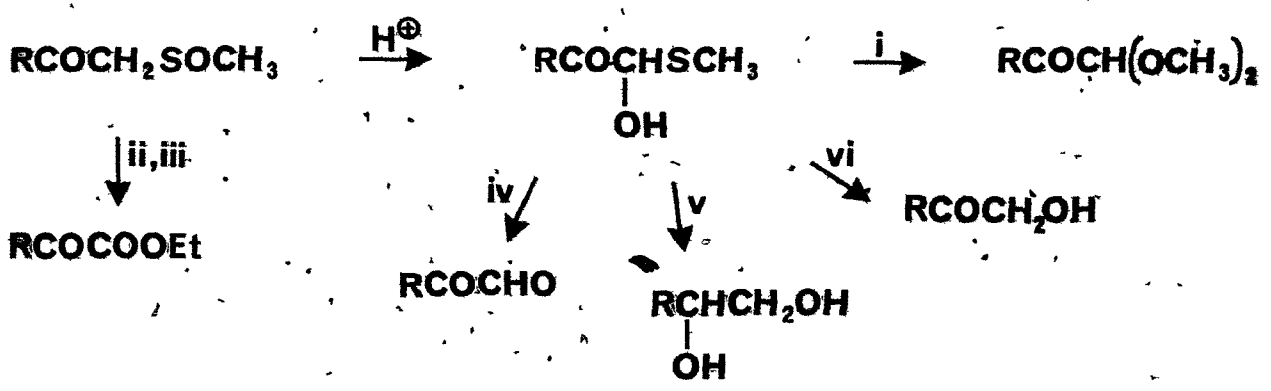
The thermal elimination of RSO_2H has also been used in order to remove the sulphur-containing moiety, the result of such a reaction being the introduction of unsaturation α,β to a ketone; such species serve as major intermediates for the elaboration of organic structures.

A potentially very useful reaction of β-ketosulphoxides is their reaction with Grignard reagents.[130] This produces a stable organometallic reagent which undergoes facile reaction with electrophiles such as ketones:

$$PhSOCH(MgX)COR + Me_2CO \longrightarrow PhSOCHCOR \quad (C(OH)Me_2)$$

As was mentioned above the alkylation of β-ketosulphoxides is a very facile process, reactions usually being carried out in DMF or THF solutions or under phase-transfer conditions.[131] A major advantage of this approach is that monoalkylation can readily be achieved[4,123] whilst alkylation of the more reactive β-

Scheme IV: Preparation of 1,2-dioxygenated compounds after Russell et al.[128]



i) I_2/CH_3OH ; ii) Br_2 ; iii) EtOH ; iv) $Cu(OAc)_2$; v) $NaBH_4$; vi) $HOCH_2SO_2^{\ominus}\,^{\oplus}Na$.

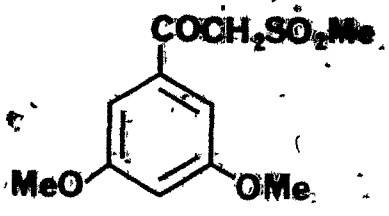
ketosulphides[119] and 1,3-diketones[118] inevitably results in the production of a mixture of mono- and dialkylated products.

The best C-S bond cleavage reaction reported for β-ketosulphones is that due to Lamm and Samuelsson[132] involving the cleavage of arylalkyl and arylaryl-β-ketosulphones by the use of electrochemical methods. The overall reaction may be represented by the following equation:

$$RCOCH_2SO_2R' + H_2O \longrightarrow RCOMe + R'SO_3H$$

Cleavage with zinc and acetic acid has also been used successfully.[123,133]

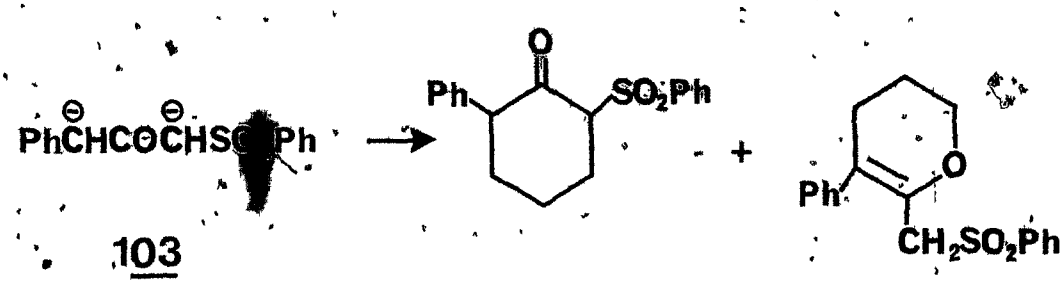
Most reactions of β-ketosulphones so far reported have used them as synthetic intermediates, as for the β-ketosulphoxides. For example Cannon et al.[134] have used **102**, synthesised from the corresponding ester and



102

the carbanion of dimethylsulphone, to introduce a 5-alkyl group, in high yield, in the synthesis of 5-n-alkyl resorcinol dimethyl ethers. Alkylation of β-ketosulphones has been carried out by both conventional methods[123,135] and under phase-transfer conditions,[136] although the latter is probably preferable.

A particularly interesting reaction of β-ketosulphones is the reaction of the dianion, **103** with 1,3-dibromopropane to give either the substituted cyclohexane, **104** or the cyclic enol ether, **105**, depending on the reaction conditions, in up to 90% yield.[137] Similar reactions have also been investigated involving β-ketosulphoxides.[119]



103 **104** **105**

The reduction of the β-ketosulphone moiety has been studied by several groups; in particular, Crumbie *et al.*[138] have used the novel reagent yeast in order to prepare optically active β-hydroxysulphones in high

yield and optical purity. Other more conventional methods include the use of sodium borohydride which yields β-hydroxysulphone[127,139] and lithium aluminium hydride which produces the corresponding β-ketosulphide.[127]

Sulphenylation of compounds with active methylene groups

Sulphenylation followed by oxidation of the sulphur atom to the sulphoxide followed by the thermal elimination of a sulphinic acid is an important method for the introduction of a carbon-carbon double bond into organic molecules. The reaction has been studied in some detail.

There are four published sulphenylation routes which are well established; these are discussed below.

1) With disulphides.

Trost has reviewed this area in some detail[140] and so little will be said here. The reaction involving disulphides gives a mixture of mono and bissulphenylated products, if both are possible. The amounts of each formed is very dependent on the reaction conditions. Grossert and Dubey [141] have shown that arylalkyl-β-ketosulphones, such as **106**, do not react with disulphides in the presence of a base strong enough to remove one of the methylene protons.

$PhCOCH_2SO_2CH_3$

106

2) With sulphenyl halides.

Kühle has written an in-depth review on the synthesis and general reactions of sulphenyl halides.[142] This review contains a short section on reactions with compounds containing active methylene and methine groups.[143]

Sulphenyl chlorides, which are the most accessible of the halides, are usually produced either by bubbling chlorine gas into a carbon tetrachloride solution of a disulphide or by the reaction of sulphuryl chloride with the disulphide under basic conditions. Normally this procedure is carried out at reduced temperatures

$$RSSR + Cl_2 \longrightarrow RSCl$$

$$RSSR + SO_2Cl_2 \longrightarrow RSCl$$

since the sulphenyl chloride is a very reactive species; it is usually used without purification. As with disulphides, it is normally rather difficult to halt the

sulphenylation at the monosulphenylated product and so a mixture of products is often the result. Grossert and Dubey[141] have shown that arylalkyl-β-ketosulphones

$$RCOCH_2R' + R''SCl \xrightarrow{\text{base}} \begin{matrix} RCOCH(SR'')R' \\ + \\ RCOC(SR'')_2R' \end{matrix}$$

like **106** always react with sulphenyl halides to give bissulphenylated products.

3) With sulphenamides

Mukaiyama et al.[144] have reported the successful use of sulphenamides to prepare selectively monosulphenylated products from active methylene containing compounds, for example 2-phenythio-malononitrile, **108** can be prepared in 55% yield with no bissulphenylated side products.

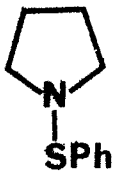
$$CH_2(CN)_2 + Et_2NSPh \longrightarrow (NC)_2\overset{\ominus\oplus}{C}NH_2Et_2 \longrightarrow PhSCH(CN)_2$$

(SPh)

107 **108**

This reaction is apparently accomplished under mild, neutral conditions i.e. room temperature for five hours in CH_2Cl_2. Other examples using N-phenylthio-

diethylamine,**107** gave 37-77% yields of the monosulphenylated adducts. If N-phenylthiopyrroldine,**109** was used in place of **107** then higher yields were realised.

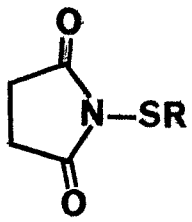


109

Grossert and Dubey[141] have used **107** to effect monosulphenylation of **106** in 90% yields under mildly basic conditions.

4) With sulphenimides.

Several groups of workers[144,145,146] have pioneered the use of sulphenimides for the sulphenylation of active methylene containing compounds. The sulphenimides used have mainly been N-alkylthiosuccinimides,**110** and N-alkylthiophthalimides,**111**, together with the



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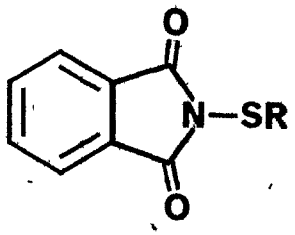


111

corresponding N-aryl compounds.

These compounds are usually made by the reaction of the parent imide with a sulphenyl halide under basic conditions[147] or by the reaction of a N-halo derivative of the imide, such as N-chlorosuccimide, with a disulphide by a radical mechanism.[148]

Sulphenylation with sulphenimides can be used to produce selectively mono or bissulphenylated products depending upon the reaction conditions for example:

$$XCH_2Y^{\cdot} + 2phtSR \xrightarrow{base} (RS)_2C\begin{matrix}X\\Y\end{matrix} + 2phtH$$

Grossert and Dubey[141,149,150] have used N-alkyl and N-arylthiophthalimides (111, R=Me, Et and Ph) to sulphenylate arylalkyl4 β-ketosulphones.

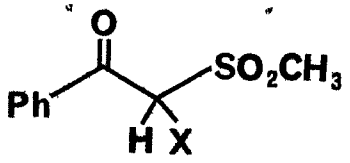
Another route to α-sulphenylated β-ketosulphones has been attempted by Grossert and co-workers.[151] This reaction initially involves the introduction of a α-halogen atom using either sulphuryl chloride or pyridinium bromide perbromide followed by attempted nucleophilic displacement of this group with a sulphur nucleophile e.g.

$$RCOCH_2SO_2R' + SO_2Cl_2 \longrightarrow RCOCH(Cl)SO_2R'$$

$$RCOCH(Cl)SO_2R' + R''S^{\ominus} \longrightarrow RCOCH(SR'')SO_2R'$$

Although it is established that α-halosulphones undergo nucleophilic substitution reactions with thiolate anions[152] it is more common for α-halosulphones to be reduced under such conditions. For example Bordwell and Doomes[153] have shown that the latter reaction occurs readily for a wide range of nucleophiles, for example RO^-, PhMgBr, RS^-, SO_3^{2-} and Ph_3P.

Grossert and co-workers[151] have studied the reaction of 2-chloro-2-methylsulphonyl-1-phenylethanone, **112** and the corresponding bromo compound, **113**, with



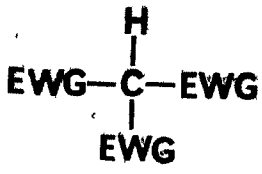
112 X = Cl
113 X = Br
114 X = SEt

ethanethiolate to form 2-ethylthio-2-methylsulphonyl-1-phenylethanone, **114**. However, they found that a mixture of products was formed and the reaction was deemed not to be synthetically useful.

$$\underset{}{\mathbf{112}} \xrightarrow{EtS^{\ominus}} \underset{57\%}{\mathbf{106}} + \underset{34\%}{\mathbf{114}} + \underset{66\%}{EtSSEt}$$

Highly substituted methanes with multiple electron-withdrawing groups.

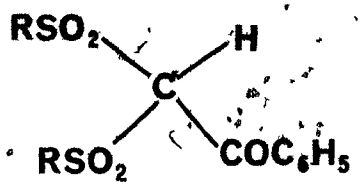
There has been much effort devoted to the synthesis of substituted methanes with multiple electron-withdrawing groups. β-ketosulphides, sulphoxides and sulphones are members of this group of compounds and have some very interesting properties due to the active methylene group which they contain; see discussion above. However, more highly substituted methanes are available synthetically and several workers have studied substituted methanes with three electron-withdrawing groups attached, **115**, where EWG can be $-NO_2$, -CO- and $-SO_2-$ amongst other groups. The interest in these compounds is mainly due to the highly activated methine proton which is usually easily removed by weak bases.



115

In 1944 Bohme and Huang[154] reported that their attempts to prepare a methane substituted with four electron-withdrawing groups had failed. They were, however, able to make **116** by reaction of bis(alkylsulphonyl)methanes with benzoyl chloride and a

base.



116

Another route to this type of complex functionality is outlined below:

$$RCOCH_2SR' + R''SX \xrightarrow{base} RCOCH(SR'')SR'$$

117

$$117 \xrightarrow{ox} RCOCHSO_2R'$$
$$\quad\quad\quad

this thesis) other examples of trisubstituted methanes with three sulphonyl groups have been prepared (compounds **48** and **55**).

Carbon acids.

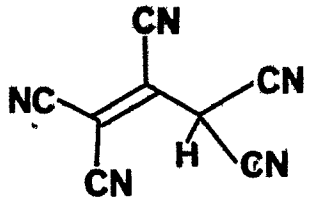
The acidity of a hydrogen-containing functional group is one of its fundamental properties and much effort has been expended in the gathering of data on such important information. These data may be obtained by a wide variety of different techniques which include conductance, optical, electrometric and other measurements. There are many standard works which describe the relevant techniques and the reader is directed to these for further information.[156,157,158] Two compilations[159,160] of the values of ionisation constants for about 5500 acids in aqueous solution have been published and a cursory glance at these volumes will convince the reader that the majority of the compounds included are oxygen and nitrogen acids. However carbon acids are not prominent in these compilations. In the last twenty years there have been a number of reviews concerning carbon acids and these have especially been concerned with the weaker acids, i.e. those acids weaker than a pK_a value of 20.[161,162] Particular interest has centred around the correlation of Hammett type parameters with pK_a values and the

interpretation of these results.

Notwithstanding the above, there have been some studies concerning strong carbon acids (pK_a < 20) and these will be discussed in turn.

In order to obtain stronger carbon acids, the attachment of electron-withdrawing groups adjacent to the ionising C-H group is required; the cyano, nitro, carbonyl and sulphonyl groups are all good candidates for this requirement.

Cyano groups have produced the most dramatic effects and simple structural modification produces a range of pK_a values from -8.5 for pentacyanopropene,[163] **118** to



118

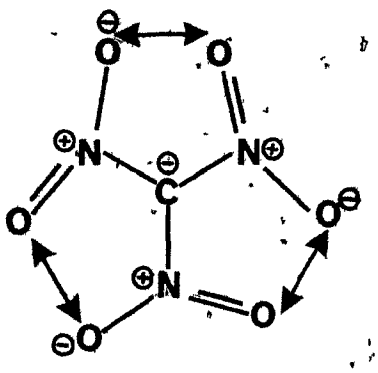
approximately 25 for acetonitrile.[164] The introduction of a cyano group adjacent to the ionising proton in a carbon acid generally increases its acidity by more than 10 pK_a units as is shown by the data in Table IV for compounds of structure $CH_n(CN)_{4-n}$.

Nitro compounds have been the most studied carbon acids (it should be noted that there is some question as

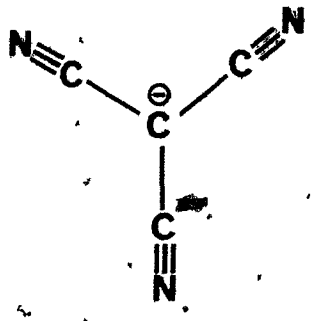
Table IV: pKa values of some carbon acids.

Compound:	pKa	ref.
$CH_n(CN)_{4-n}$:		
CH_4	~46	165
CH_3CN	~25	166
$CH_2(CN)_2$	11.20	167
$CH(CN)_3$	-5.13	162
$CH_n(NO_2)_{4-n}$:		
CH_4	~46	165
CH_3NO_2	10.2	168
$CH_2(NO_2)_2$	3.63	160
$CH(NO_2)_3$	0.14	160

to whether nitro groups are carbon or oxygen acids[164] with the exception of hydrocarbons themselves and Table IV also shows the pK_a values for the series $CH_n(NO_2)_{4-n}$. As can be seen from this table the introduction of the first nitro group has a much larger effect than in the case of a cyano group whilst introduction of further nitro groups has progressively less effect again in contrast to that observed for the cyano group. In the case of the nitro group this has been termed a 'saturation effect'[166] and is due to steric crowding around the central carbon atom with series O-O non-bonding interactions, see **119**. For cyano groups this crowding is not evident since the cyano group is linear, **120**.



119



120

The acidities of the dinitroalkanes, **121** have been

$$RCH(NO_2)_2$$

121

studied in detail by several groups.[169-171] These workers have attempted to correlate the pK_a values of these compounds with the Taft σ^* parameters for the substituent R. Similar correlations have been successful for a series of amines, RNH_2 where a plot of pK_a *vs* σ^* for R gives a straight line with a slope in the range 2.6-3.3.[172] Tselenskii *et al.*[168,173] have used the pK_a values of eighty-one compounds of type **121** to obtain a good linear relationship, *viz*: $pK_a = 5.23 - 3.29\ \sigma^*$. The slope of 3.29 fits within the range for the series of amines where the substituent is directly attached to the atom bearing the ionising proton and is apparently in the range expected[174] for any such series of compounds. Some of the dinitromethanes do not fit this correlation well and this has been explained in terms of steric effects which decrease conjugation in the anion.[173]

The acidities of ketones have been studied in much less detail than nitro and cyano containing compounds one reason for this being that ketones often exist in two forms, enol and keto, which have dramatically

different pK_a values. For example, the enol form of cyclopentanone in water has a pK_a value of 11.8 whilst the keto form has a pK_a of 16.4.[175] However, since β-diketones are important bidentate ligands to the organometallic chemist their pK_a values have been investigated.[176,177] These compounds exist as both keto and enol tautomers and most of the pK_a values of these lie in the range 8-12, with the enol tautomers (oxygen acids) being more acidic as expected. The variation of the substituent, R in **122** as well as R' affects the pK_a values in a predictable manner.[178] The

122

pK_a results obtained for the keto form of six substituted acetylacetones (i.e. **119** with R'=Me) by Schwarzenbach and Felder[179] and by Rumpf and La Riviere[180] correlate with σ^*, viz. $pK_a = 10.53 - 1.62\,\sigma^*$. The correlation coefficient is 0.977 which is very good by Jaffé's[181] criteria. Note that the slope of the line is outside the expected range (see above discussion).

For substituted ethyl-3-oxobutanoates, **123**, the pK_a values[182] of five compounds (R=H, Me, Et, nPr and Ph)

123

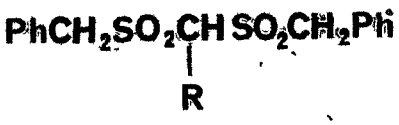
also give a good straight line, viz. $pK_a = 12.57-3.21\sigma^*$, with a correlation coefficient of 0.979. The above equation differs from that reported in the literature[174] since the σ^* value for phenyl substituent is 0.75[183] and not 0.6 as used in that study.

1,3-Disulphones are less acidic than 1,3-diketones; for example, bis(methylsulphonyl)methane has a pK_a of 12.50 [184] whilst the keto form of acetylacetone has a pK_a of 8.85 [180] under similar conditions. The pK_a values of three bis(ethylsulphonyl)methanes **124** (R=H, Ph and Br)

124

give the excellent correlation with σ^* viz. $pK_a = 2.55-0.65\sigma^*$, with a correlation coefficient of 0.999, using the data of Bell and Cox.[185]

Ang and Lee[186] have also reported the pK_a values of four substituted dibenzylsulphonyl methanes, **125** (R=H,Ph, $pCN-C_6H_4$ and $pNO_2-C_6H_4$) and these results



125

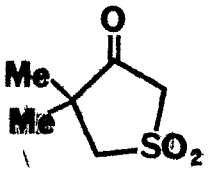
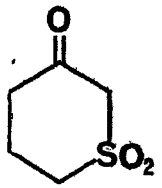
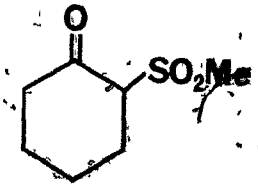
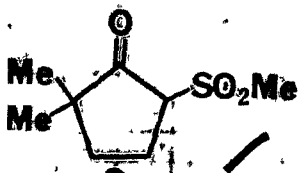
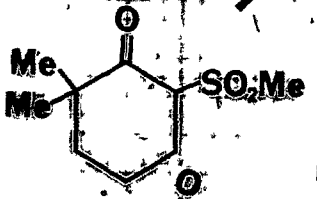
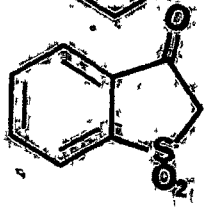
again correlate well with the σ^* parameters of the substituents in the form $pK_a = 14.48-5.11\,\sigma^*$ (correlation coefficient = 0.979).

β-Ketosulphones, as would be expected, show pK_a values intermediate between 1,3-diketones and 1,3-disulphones. For example, the pK_a value of **126** is 9.9 [187] in water at 25°C and this falls between the

126

values quoted above for bis(methylsulphonyl)methane and acetylacetone under similar conditions. Holst and Fernelius [188] have reported the pK_a values of three β-ketosulphones in dioxane-water mixtures and these results are presented in Table V. Truce et al.[187] have also studied the pK_a values of β-ketosulphones and their results for ten compounds of this type are also presented in Table V. No study has been reported which considers the effects of a range of substituents on the

Table V: pKa values for some β-ketosulphones after Truce et al.[187] unless otherwise indicated.

Compound:	pKa
$PhSO_2CH_2COPh$	9.83 ± 0.02[+]; 12.9[†]
$MeSO_2CH_2COPh$	10.01 ± 0.02[+]; 10.7[†], 12.9[‡]
$PhSO_2CH_2COMe$	10.09 ± 0.02[+]; 10.9[†]
$MeSO_2CH_2COMe$	10.48 ± 0.01[+]; 9.90[†] ± 0.02
	5.83 ± 0.04[*]
	9.01 ± 0.02[*]
	10.46 ± 0.02[*]
	10.70 ± 0.03[*]
	11.62 ± 0.03[*]
	7.65[*‡]

[+]75% dioxane-25% water [188], [†]50% dioxane-50% water [188]

[‡]50% ethanol - 50% water, [*] water, [‡]ref 189

pK_a values of β-ketosulphones as is the case for 1,3-diketones and other species as discussed above.

Aims of the present study.

In the current work the initial aim was to prepare a new range of sulphenylated β-ketosulphones and to characterise them using the usual techniques. It was also an aim to investigate some reactions of these compounds, in particular, reactions leading to α-sulphenylated-β-ketosulphones (S-oxidised α-ketomercaptals) and to derivatives at the keto group. In addition, reactions of 1,3-dianions across the sulphonyl group were of interest. Finally, since these compounds are strong carbon acids ($pK_a < 20$) the pK_a values for a series of such compounds were to be measured and interpreted.

CHAPTER 5

RESULTS AND DISCUSSION

In this chapter the preparation and properties of a new range of β-ketosulphones and their derivatives are discussed. One of the reasons for preparing these compounds was that they are potentially useful biologically active compounds.

Many organic sulphur-containing compounds have been synthesised which are natural product analogues. For example, natural product analogues of nucleotides,[190] sugars[191] and proteins[192] have been prepared and some of these have considerable biological activity.[191] Also it has long been known that soaps have some insecticidal properties, for example, the old practise of throwing spent dish-water on roses to kill aphids.[193] Recently, research in this area by Puritch[194,195] has shown that fatty acids and their potassium salts have useful insecticidal activity against the balsam woolly aphid. Fatty acids and their esters (e.g. those of sucrose and sorbitan) have been shown by Ando et al.[196,197] to have some anti-tumor activity. Other useful properties have also been attributed to such compounds, for example Kabara[198] has shown that glycerol monolaurate has high anti-microbial activity against gram-positive organisms.

All the compounds prepared in the current study are relatively strong carbon acids (the measurement of their pK_a values will be discussed later in this chapter) and they all have some natural product character since they contain long-chain fatty residues and pyridine and pyrrole rings. The long-chain compounds can be thought of as carbon acid analogues of regular fatty acids.

It is thus intended that the prepared compounds should be screened for possible biological activity. Initial results indicate that aqueous ethanol solutions of some of these compounds, especially the more acidic ones, and their potassium salts show some activity towards the bacterium S. Lutea.* Further testing of these compounds is underway.

Since the long-chain containing β-ketosulphones and their derivatives have structures similar to detergents they may be usefully employed in such a capacity. Work-up procedures involving these compounds have often led to emulsions being formed indicating that the above suggestion may prove useful. It should be noted that simple β-ketosulphoxides have been patented by Proctor and Gamble in the United States as detergents.[199]

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* The author wishes to thank Dr. A. Taylor and his staff, of ARL-NRC, Halifax, N.S. for these results.

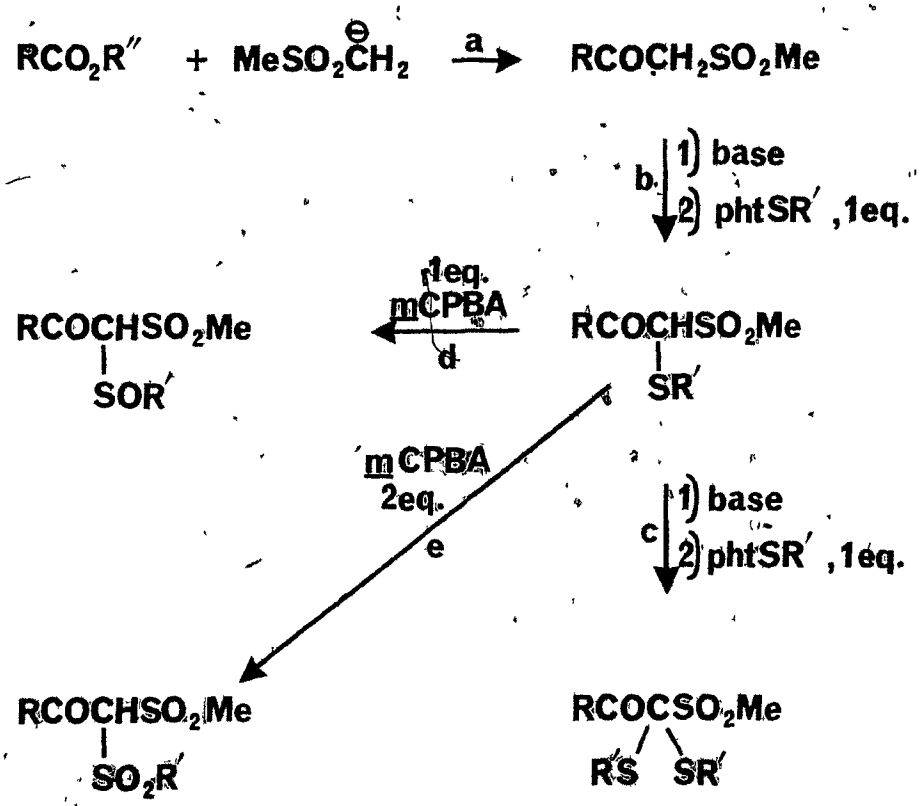
Preparation and spectral properties of β-ketosulphones and their derivatives.

The proposed sequence of reactions to be undertaken are presented in Scheme V starting from a general ester, RCO_2R''. Grossert and Dubey have employed a similar procedure using ethyl benzoate as the starting ester.[141,150,155] Such a scheme has not been exploited for other esters and so was investigated in the present study for a series of long-chain fatty esters amongst others.

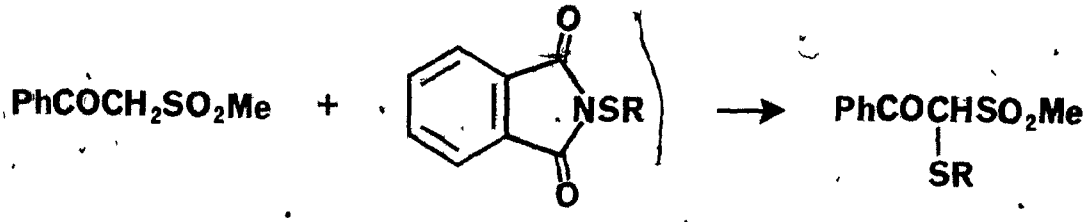
Step a, in the scheme, has been used previously by House and Larson[123] for R=alkyl and by Grossert et al.[73] for R=Ph. This step proceeded in high yield for all esters with R=alkyl by the reaction of the anion of dimethyl sulphone with an ester in dimethyl sulphoxide or tetrahydrofuran under a dry nitrogen atmosphere. In order to obtain high yields of these compounds it was necessary to carefully control the temperature of the reaction mixture since those in excess of 55°C produced significant decomposition.

Step b, the monosulphenylation of a β-ketosulphone using a sulphenimide, **111** (where R=Me,**111a**, Et,**111b** or Ph,**111c**) in the presence of triethylamine is a pathway unique to this laboratory in which the author has worked. Grossert and Dubey[150] have used a similar route to sulphenylate arylalkyl-β-

Scheme V:


RCO2R″ + MeSO2CH2⊖
a
RCOCH2SO2Me
b
1) base
2) phtSR′ ,1eq.
RCOCHSO2Me
SR′
1eq. mCPBA
d
RCOCHSO2Me
SOR′
mCPBA 2eq.
e
c
1) base
2) phtSR′ ,1eq.
RCOCHSO2Me
SO2R′
RCOCSO2Me
RS SR′

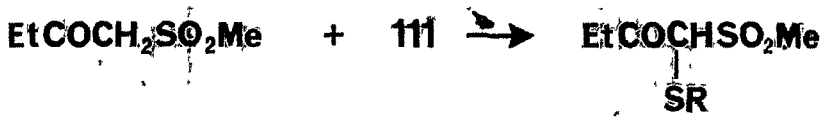
ketosulphones such as **106** producing **127** in good yield.



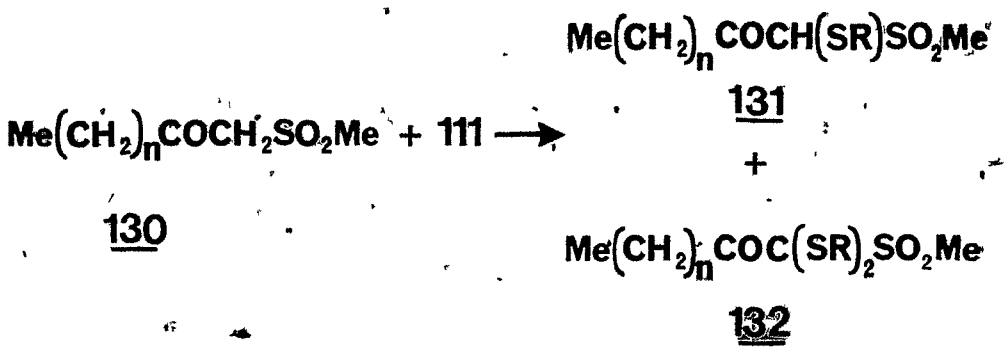
106 **111** **127**

It should be noted that the phthalimide-derived sulphenylating agents **111** are used in preference to the related succinimide derived compounds **110** since the phthalimide remaining, after the reaction is complete, is much less soluble in organic solvents than is succinimide.

The monosulphenylation of **128** with **111** producing **129** proceeded in high yield whilst a similar reaction involving the long-chain β-ketosulphones, **130** and **111a** and **111b** produced a mixture of monosulphenylated, **131** and bissulphenylated **132** products in about 40% and 30%



128 **129**

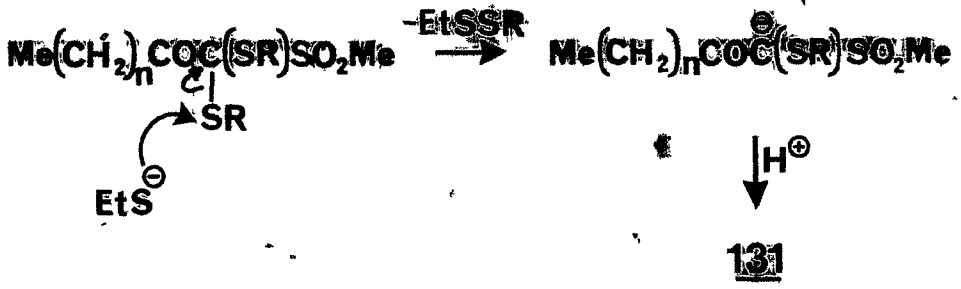


yields respectively. These mixtures could be separated with considerable difficulty by shaking with a series of buffers or by the use of column chromatography. This approach was therefore abandoned in favour of that described below.

Combination of steps b and c in Scheme V to produce the bissulphenylated β-ketosulphones, **132** directly, proceeded in yields greater than 90%. The monosulphenylated products **131** were then easily obtained by the reaction of the bissuphenylated compound with ethanethiolate in dry tetrahydrofuran in the presence of excess sodium hydride; this method was initially developed by Grossert and Dubey.[141,150]

The mechanism of this reaction, which yielded exclusively monosulphenylated β-ketosulphones, presumably involves direct attack by the thiolate anion on the sulphenyl sulphur atom in **132** to yield the stabilised anion (page 118) which cannot be protonated

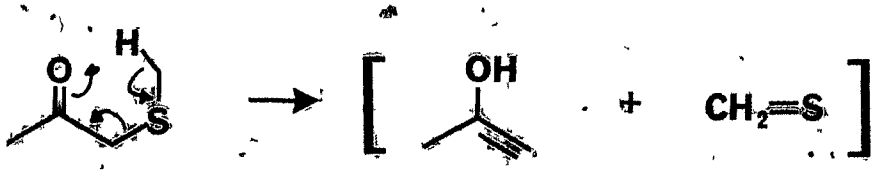
under the reaction conditions of excess sodium hydride.



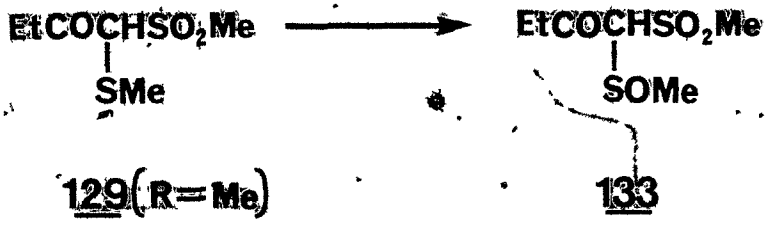
Hence the anion does not undergo further reaction with ethanethiolate and one methylthio group is selectively removed from **132** in high yield.

Monosulphenylations using N-phenylthiophthalimide, **111c** proceeded cleanly in high yields with no control problems; hence recourse to the route described above was not required.

The monosulphenylated compounds, **129** and **131** decompose if kept at room temperature and so they were stored under refrigeration. The following scheme is suggested for this decomposition:



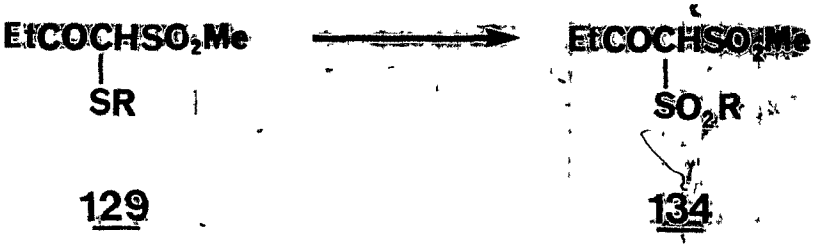
Oxidation of **129** (R=Me) to the sulphoxide **133** using m-chloroperoxybenzoic acid (step d) was undertaken and



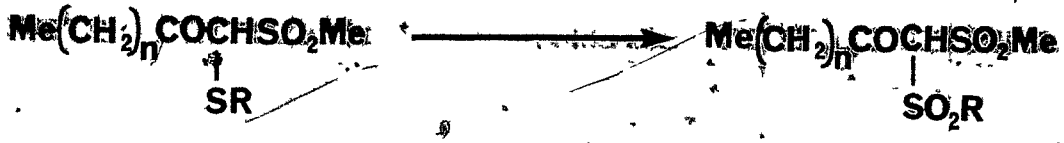
129(R=Me) 133

the product was realised in only about 40% yield. This product decomposed rapidly and was identified only by its proton nmr spectrum. Grossert and Dubey[155] have found similar problems with the corresponding phenylsulphoxide, prepared by the sulphenylation of **106** with **111c** followed by oxidation, so in the current study the isolation of this type of compound was abandoned. A similar mechanism to that described above for **129** and **131** can be used for the decomposition of **133**.

Step e, the oxidation of the monosulphenylated β-ketosulphones, **129** and **131** to the corresponding S,S-dioxides **134** and **135**, using two molar equivalents of m-



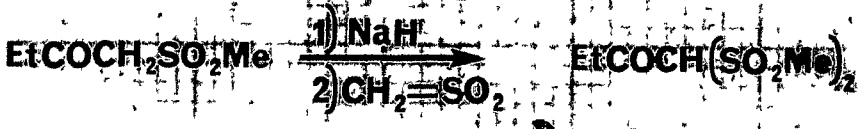
129 134



131 135

chloroperoxybenzoic acid in methylene chloride under a dry nitrogen atmosphere proceeded readily in high yield. Oxidation of sulphides to sulphones is generally carried out by the use of hydrogen peroxide-acetic acid mixtures and although this method was attempted, the reaction was not found to be useful since the products are fairly water soluble and could only be isolated with some difficulty.

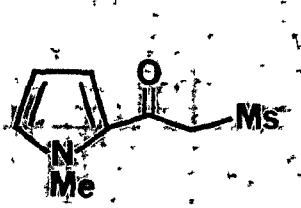
Preparation of **134** (R=Me) was also attempted in one step from **128**. This involved the formation of the anion of **128** using sodium hydride followed by attempted reaction with sulphene and was expected to proceed thus:



128

Durst[200] has shown that 1,3-diketones undergo a similar reaction; however, no useful products could be identified from this reaction in the present study.

The β-ketosulphones containing a N-methylpyrrole ring, **136** and pyridine rings (**137** and **138**) were also



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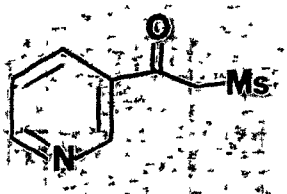

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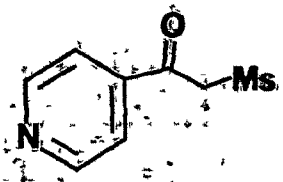
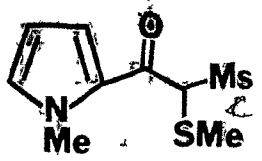


138

prepared in the present study by reaction of the corresponding ester as in Scheme V. The reactions to form **137** and **138** did not proceed in very high yield. These compounds are slightly water soluble and also seemed to hydrolyse much more readily than the other β-ketosulphones. The ester, 2-carboethoxypyrrole did not yield an isolable product but instead polymerised under the reaction conditions. In addition, reactions with the anion of dimethyl sulphone and the N-oxides of ethyl nicotinate and ethyl isonicotinate failed and starting materials were recovered quantitatively in both cases. Presumably the ester group in these molecules is deactivated by the pyridyl ring.

Monosulphenylation of **136** with either N-methylthio- or N-phenylthiophthalimides (**111a** and **111c**) yielded the products **139** and **140** with no trace of the corresponding bissulphenylated compounds. These compounds could be



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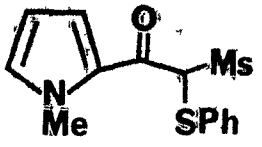
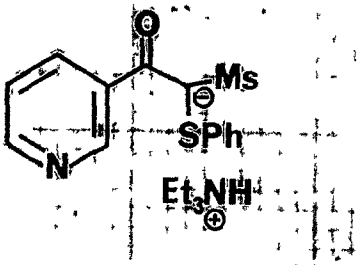


140

easily oxidised with m-chloroperoxybenzoic acid to produce the corresponding S,S-dioxides.

Sulphenylation of either **137** or **138**, even with excess sulphenylating reagent, did not yield the usual products. The reactions of **137** and **138** with **111a** both yielded oils which could not be fully characterised whilst the reactions with **111c** gave the triethylammonium salts **141** and **142** respectively.



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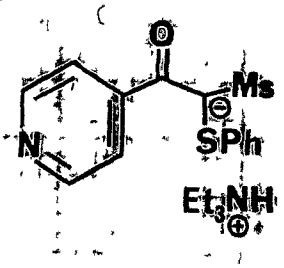


142

The proton nmr spectra of these compounds fit with the structures given, however, the carbon-13 nmr spectra are rather novel. Most of the resonances in this spectrum, run in $CDCl_3$ at ambient temperature on the CFT-20 spectrometer, were broad and broad lines in a carbon-13 spectrum are rare. An investigation of the triethylamine salt of the corresponding phenyl compound i.e. **143** made *in situ* by addition of one equivalent of

143

triethylamine to the sulphenylated β-ketosulphone in an nmr tube also produced a similar broadened spectrum. Addition of excess triethylamine sharpened all the lines of this spectrum thus suggesting that different components of an equilibrium mixture were present. This was confirmed by addition of excess triethylamine to the solutions of **141** and **142**.

This hypothesis could be tested by cooling the solution which would be expected to produce a carbon-13 nmr spectrum showing resonances for both species present, rather than an average spectrum as described above. For experimental reasons it was preferable to run the carbon-13 spectrum at a higher field as well as at a

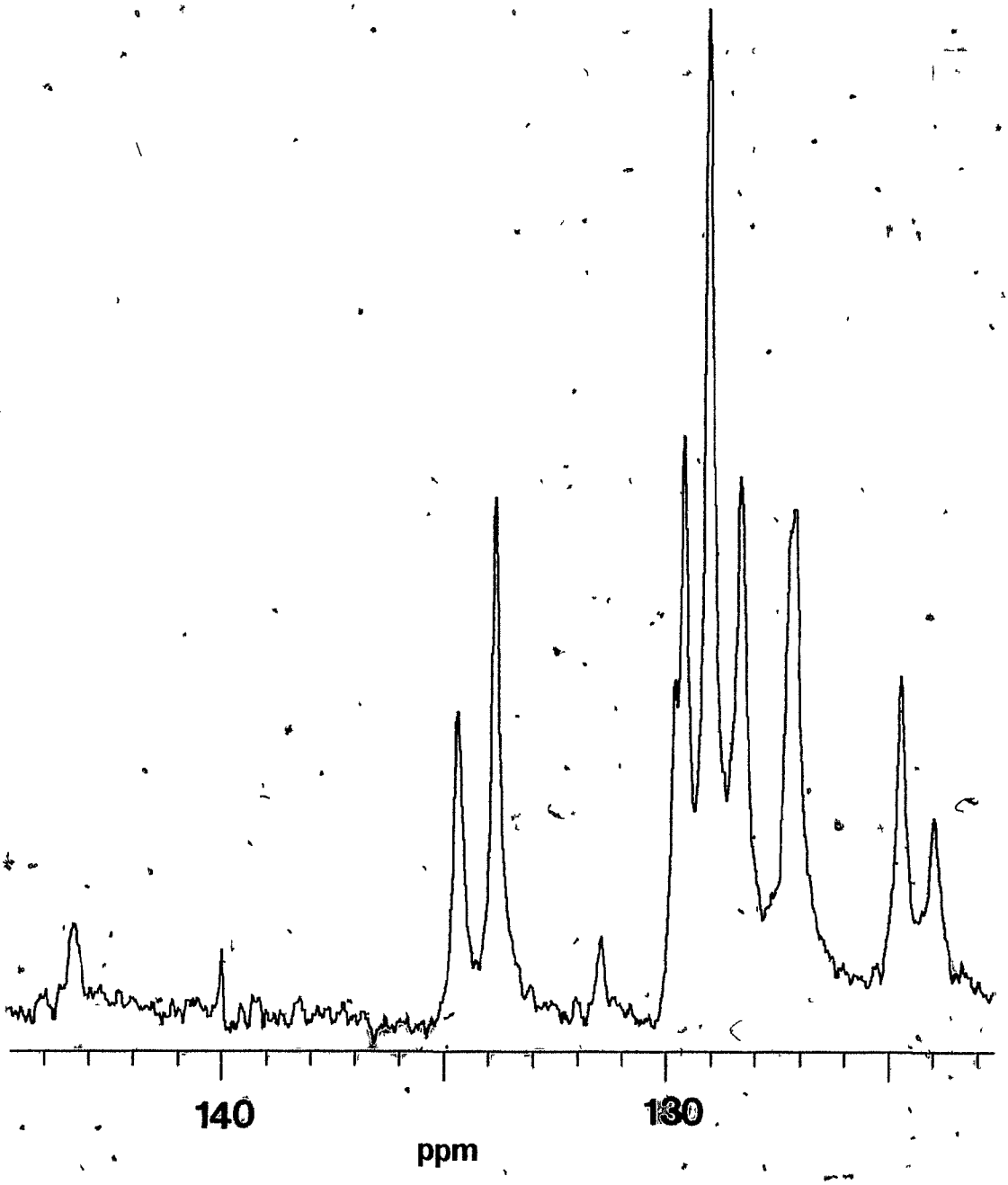
lower temperature. This combination enabled the spectra to be interpreted more easily and was carried out using **143** since it was more easily handled and was available in large quantities. A carbon-13 nmr spectrum of the parent compound **144** was obtained at ambient temperature

144

(18° +· 1°C) and this exhibited normal width resonances which were unchanged on cooling to -60°C (the aromatic region of this spectrum is reproduced in Figure VIII). The methylsulphonyl peak at 37.79 ppm was sharp. On addition of one equivalent of triethylamine and after one hour to allow equilibration, the carbon-13 nmr spectrum was again obtained at ambient temperature. Figure IX shows the aromatic region of this spectrum; as can be seen the resonances are all broadened and the number of lines is increased. The aliphatic region now showed two peaks due to methylsulphonyl groups at 37.84 and 42.45 ppm plus a peak at 91.49 ppm. The 'carbonyl region' also showed two peaks at 186.84 and 189.95 ppm, the latter being identical in position to the carbonyl peak of **144**. Cooling this sample down to -60°C dramatically sharpened all the resonances in the

Figure VIII: Aromatic region of the carbon-13 nmr spectrum of **144** at 18°C

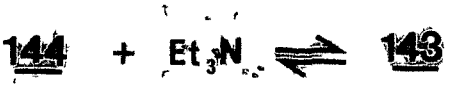
Figure IX: Aromatic region of the carbon-13 nmr spectrum of **144** + 1 equivalent of triethylamine at 18°C



aromatic region and caused the appearance of two more lines, as shown in Figure X.

Addition of a large excess of triethylamine (3 molar equivalents) again altered the spectrum dramatically. Only about half the peaks remained in the aromatic region (see Figure XI), there was only one methylsulphonyl peak, at 41.83 ppm and only one peak in the 'carbonyl' region at 186.65 ppm. The peak at approximately 90 ppm also remained. This last spectrum was changed very little by running at a lower temperature.

This series of spectra shows the equilibrium:



The initial spectrum with no triethylamine present shows the resonances of **144** whilst the final spectrum shows those for **143**, the intermediate spectra are for an equilibrium mixture of the two with the low temperature spectrum (Figure X) showing the resolved spectra for the two species overlapping. Of course **143** is an enolate anion and so the structure shown above is only one of the possible canonical forms. The above discussion also applies to the interpretation of the spectra of the salts **141** and **142**.

Figure X: Aromatic region of the carbon-13 nmr spectrum of **144** + 1 equivalent of triethylamine at -60°C

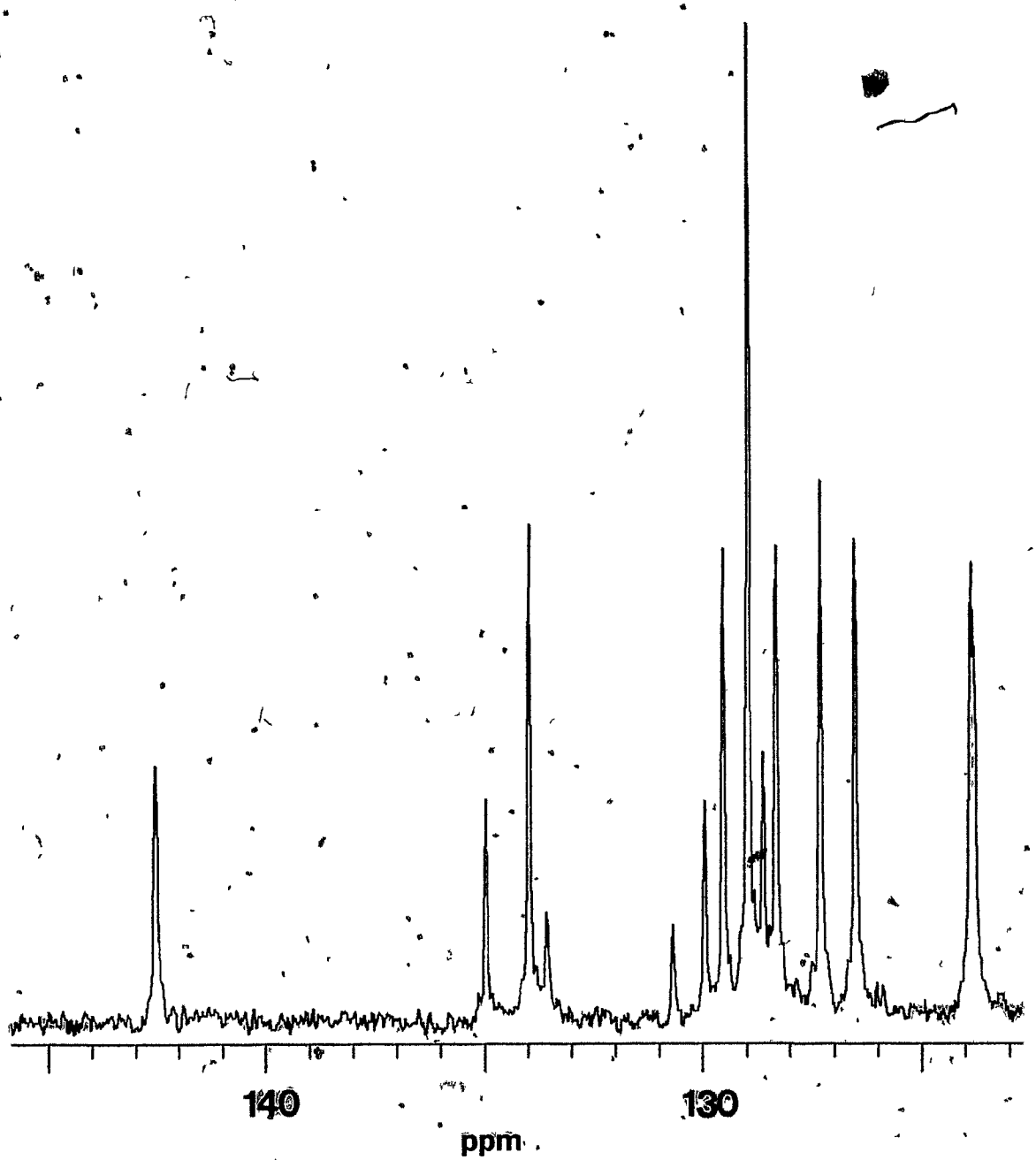
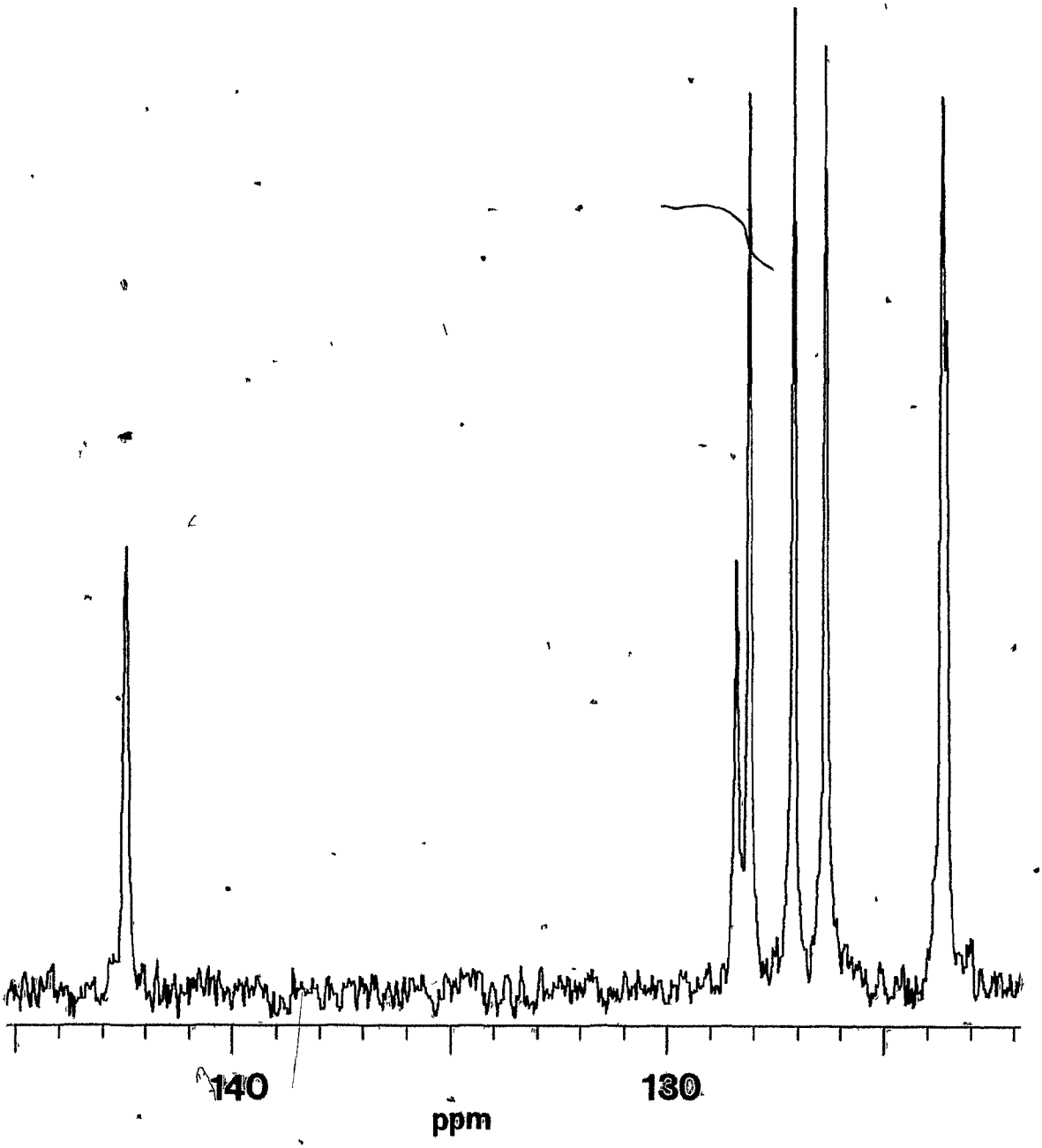
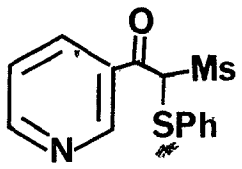


Figure XI: Aromatic region of the carbon-13 nmr spectrum of 144 + 3 equivalents of triethylamine at -60°C



The mass spectrum of **141** run at 70eV showed no ions above m/z 307. This ion corresponds to $C_{14}H_{13}NO_3S_2$, **145**$]^+$. However, careful control of the probe temperature and ionisation voltage enabled triethylamine to be detected at an ionisation voltage of 20eV and a probe temperature of 60°C. This was also true for **142** and thus suggested a way of obtaining the monosulphenylated β-ketosulphones **145** and **146**. Such a method would involve



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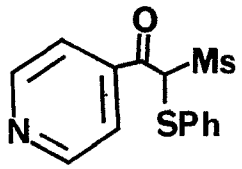
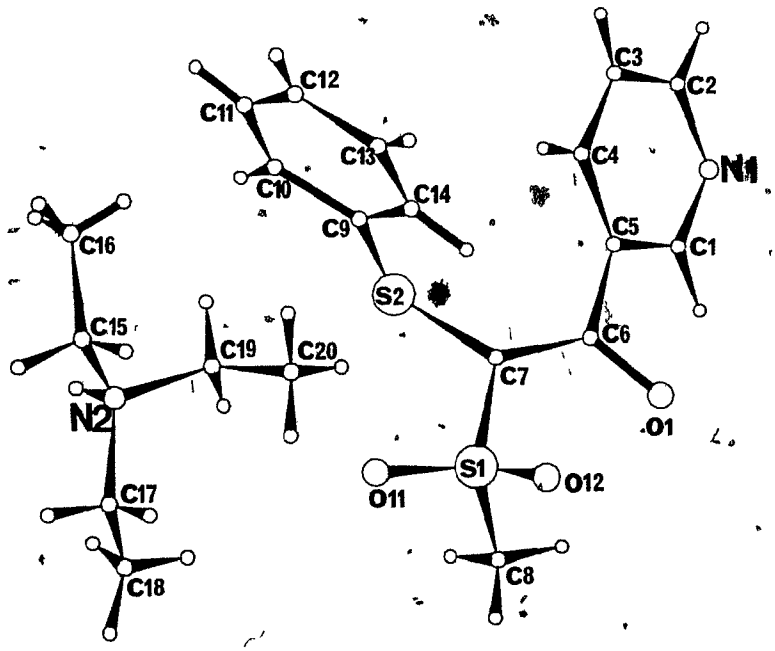


146

careful warming of the salts **141** and **142** under vacuum, as was done in the mass spectrometer. This was attempted and triethylamine was indeed collected in an ice-cold trap, but unfortunately the residue decomposed and no useful quantities of **145** or **146** could be isolated.

The structure of **141** was determined using X-ray diffraction methods and a projection of the structure obtained is presented in Figure XII. The complete crystal data and bond tables are given in the Experimental Section and in Appendix III together with a stereoscopic projection of the unit cell.

Figure XII: X-ray structure for **141** .



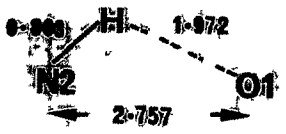
The C-S bond lengths in compound **143** are 1.744(3)Å (C7-S1) and 1.755(3)Å (C8-S1) for the sulphone-bonded carbon atoms and 1.734(3)Å (C7-S2) and 1.770(3)Å (C9-S2) for the sulphide bonded carbon atoms. These data should be compared with the C-S bond length in dimethyl sulphone (1.774(3)Å[72]) and the typical C-S bond in a sulphide (1.817(5)Å[201]). All these bond lengths in **143** are shorter than the literature values given, thus implying some additional double-bond character in each case.

The S-O bond lengths in the sulphone group are slightly different, but have an average value of 1.440(4)Å which is very close to the average accepted for such bonds (1.439(4)Å[73]). It is not clear why the two S-O bond lengths are apparently different.

The C6-C7 bond length is 1.396(4)Å which should be compared with 1.537(5)Å for a carbon-carbon single bond[201] and 1.335(5)Å for a carbon-carbon double bond.[201] Thus the bond has an appreciable amount of double bond character. The C6-O1 bond (1.263(3)Å) is longer than the usual carbon-oxygen double bond length (1.215(5)Å[201]) but is appreciably shorter than the typical carbon-oxygen single bond length (1.426(5)Å[201]).

The central unit, around C-7, is nearly planar with bond angles close to 120°. From inspection of the stereoscopic projection of the unit cell (given in

Appendix III) it can be seen that the HN2 bond is directed towards O1 with a H-O1 interatomic distance of 1.972(26)Å, whilst the H-O3 distance is 2.600(26)Å. These atomic positions indicate that a hydrogen bond is formed between the hydrogen atom on the ammonium nitrogen to the enolate-like oxygen atom (O1). The chief criterion for the existence of a hydrogen bond is that the hydrogen-oxygen distance should be shorter than the sum of the van der Waals' radii for these atoms.[202] The sum of these radii is 2.60Å[203] which thus indicates the presence of a hydrogen bond in this case. The NHO angle is also important and calculation shows that this is 166° *viz.*

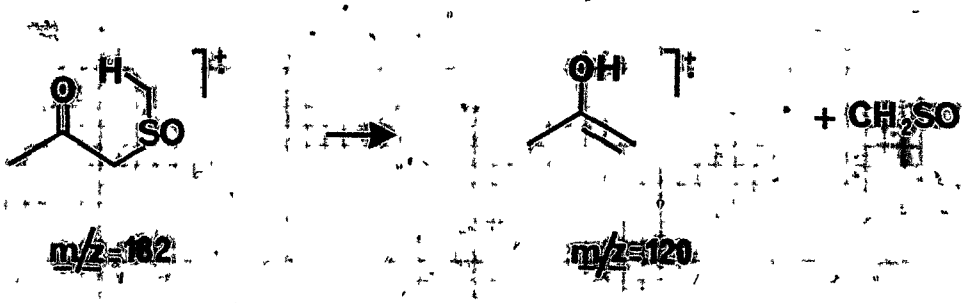


Holst and Fernelius [188] have demonstrated that β-ketosulphones show no significant enolisation and this has been confirmed by Grossert *et al.*[73] for some arylalkyl- β-ketosulphones such as **106**. In the current study infra-red spectra of KBr discs and chloroform solutions of the β-ketosulphones prepared have shown no enol to be present (*i.e.* there are no signs of an OH band at 3600-3400 cm^{-1} and the carbonyl peaks are fairly

sharp). This observation is also true for the monosulphenylated products and their oxidised derivatives.

The methylene and methine protons in the β-ketosulphones or their monosulphenylated derivatives described in this section are not exchanged with D_2O in chloroform solution as evidenced by proton nmr studies. However, addition of triethylamine results in rapid exchange of these protons. The addition of trifluoroacetic acid to chloroform solutions of **128**, **129** or **134** resulted in no observation indicating enol formation in their proton nmr spectra.

Oliver and Kinstle[204] have studied the mass spectral fragmentation of β-ketosulphones, sulphoxides and sulphides. These workers have shown that whilst β-ketosulphides and sulphoxides exhibit fairly large peaks due to a McLafferty-type rearrangement viz.



β-ketosulphones give no such peak. In the present study the mass spectra of many of the compounds made were obtained and that of **128** and the other unsubstituted β-ketosulphones, **130**, confirm the results of Oliver and

Kinstle. The mass spectra of **129** and other monosulphenylated, β-ketosulphones, **131** show peaks at M-78 which could be attributed to a McLafferty-type rearrangement from the β-ketosulphone fragments of the molecules. The β-ketosulphide fragment of the same molecule does not give a peak at M-46 which would be expected for the loss of CH_2S. Both of these observations are opposed to the simple rule suggested by these earlier workers and thus the current work suggests that this rule is only applicable to the simple β-ketosulphones, sulphoxides and sulphides studied by the earlier workers. Table VI shows the data discussed above for comparison purposes. The other major peaks in the mass spectra of these compounds are the peaks due to the fragmentation of the C-CO bonds. The peaks due to the molecular ion for these compounds are not very intense.

The proton nmr spectra of these compounds show no unusual features and the chemical shifts for the most acidic protons in **128** and its derivatives are:

compound:	δ(ppm):
128	4.06
129	4.49
133	5.18
134	5.38

Table VI: Some mass spectral data for β-ketosulphones

compound:	Intensity ratio $(M^+-MeSO_x)/M^+$	x
$PhCOCH_2SO_2Me$	0 *	2
$PhCOCH_2SMe$	0.13 *	0
$PhCOCH_2SOMe$	3.74 *	1
$EtCOCH_2SO_2Me$	0 +	2
$EtCOCH(SMe)SO_2Me$	0.67 +†	2
$EtCOCH(SO_2Me)_2$	3.94 +	2

* data form Oliver and Kinstle.[204]

\+ data from present study.

† no peak at M-46 for loss of CH_2S.

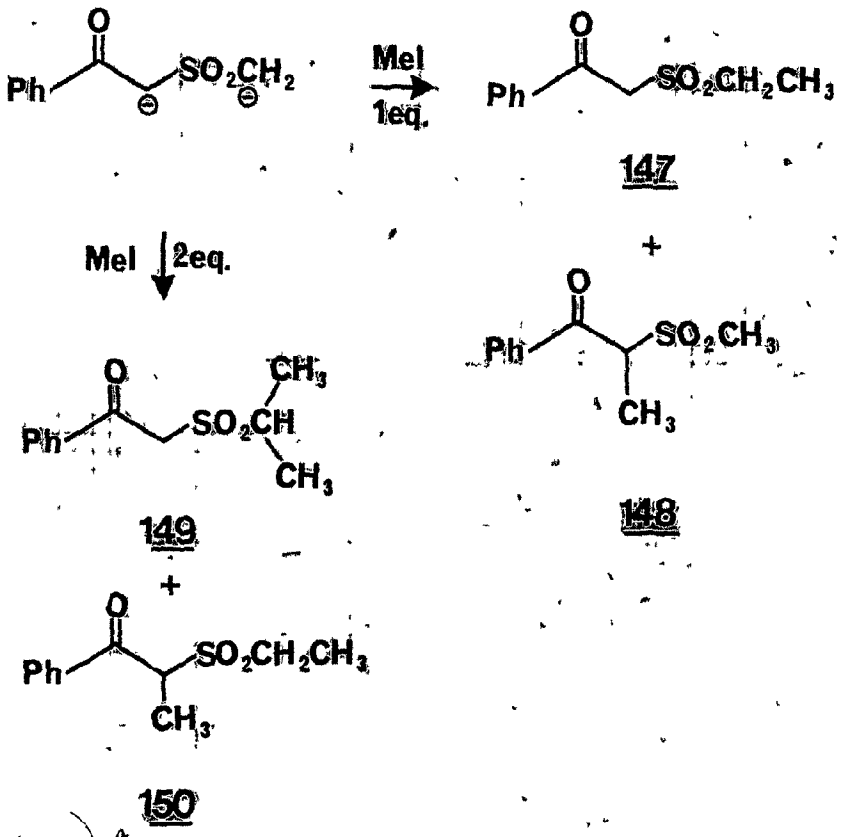
These chemical shifts increase as the electron-withdrawing ability of the substituent increases as would be expected (i.e. H << SMe < SOMe < SO_2Me). The carbon-13 chemical shifts for the carbon atoms to which these protons are attached also increase in the same order, viz. 63.42 for **128**, 73.87 for **129** and 85.73 for **134**.

Reactions of a β-ketosulphone dianion.

The study of the chemistry of a 1,3-dianion across the sulphonyl group of a β-ketosulphone, in this case **106**, is a natural extension of earlier work carried out by Grossert et al.[205] concerning the reactions of a dianion across a sulphide. The chemistry of 1,3-dianions across ketones has been studied by several groups in some detail[206,207] whilst reactions of 1,3-dianions across the ketone of a β-ketosulphone[137] and β-ketosulphoxides[208,209] are less well developed. The chemistry of 1,3-dianions across simple sulphones have been investigated[3,4,210] but very little has been reported concerning the reactions of a 1,3-dianion across the sulphone in a β-ketosulphone.[4]

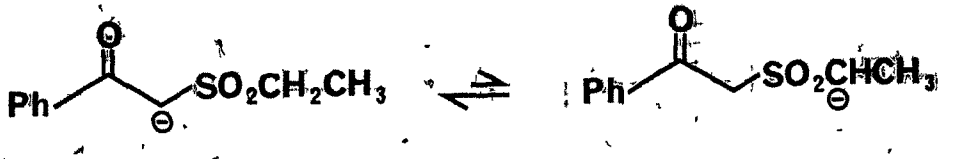
The dianion of **106** was best formed by reaction with one molar equivalent of sodium hydride in tetrahydrofuran or dimethoxyethane under dry conditions, followed by addition of one molar equivalent of n-butyl

lithium. Reaction of this dianion with one molar equivalent of methyl iodide produced **147** as the major product with a trace of **148** also. The terminal anion is



the more reactive of the two sites and so one would expect **147** to be the major product. Reaction of the same dianion with two molar equivalents of methyl iodide produced about one-third of the di-terminally alkylated product **149** whilst the major product was the 1,3-dialkylated compound **150**. In this reaction

monoalkylation will occur as above i.e, mainly on the terminal anion and thus the remaining mono-anion, **151** must be in equilibrium with **152**, the latter being the more reactive. However, this equilibrium will be largely displaced towards **151**. Compound **149** is formed by alkylation of the more reactive anion **152**.



151 **152**

The alkylation of 1,3-dianions across ketones with α,ω -difunctional electrophiles has led to the formation of carbocyclic ring systems[206] and thus a similar type of reaction was attempted in the present study in order to try and prepare cyclic sulphones. The reaction of the 1,3-dianion of **106** with 1,2-dibromoethane and 1,3-dibromopropane led to non-cyclic products. Reaction of this dianion with 1-bromo-3-chloropropane however, resulted in terminal monoalkylation producing **153**. Cyclisation was not possible until the chlorine atom had been replaced by iodine. The iodide, **154** could be cyclised to give **155**, most readily using phase-transfer conditions although traditional conditions, such as

anion formation using sodium hydride could also be used. The reactions described here are shown in Scheme VI. Some reactions of **155** were investigated.

Chlorination of **155** could be achieved readily, producing **156**, by reaction of its anion with N-chlorosuccinimide. Other halogenation reactions using regular halogenating reagents such as sulphuryl chloride, with and without triethylamine, and bromine were attempted but were unsuccessful. This is in contrast to the facility of such reactions for acyclic β-ketosulphones such as **106**.[73]

Hydrolysis of **155** with potassium hydroxide in aqueous ethanol yielded thiane-1,1-dioxide which was identified by a mixed melting point with an authentic sample.* A similar reaction involving **156** produced 2-chlorothiane-1,1-dioxide, **157**, in 94% yield, which was again identified by a mixed melting point.*

The method presented above is a facile, high yield synthesis for 2-substituted thiane-1,1-dioxides as exemplified by the preparation of **155** and **157**. In the past the preparation of thiane-1,1-dioxides has been considered in some detail due to the extensive

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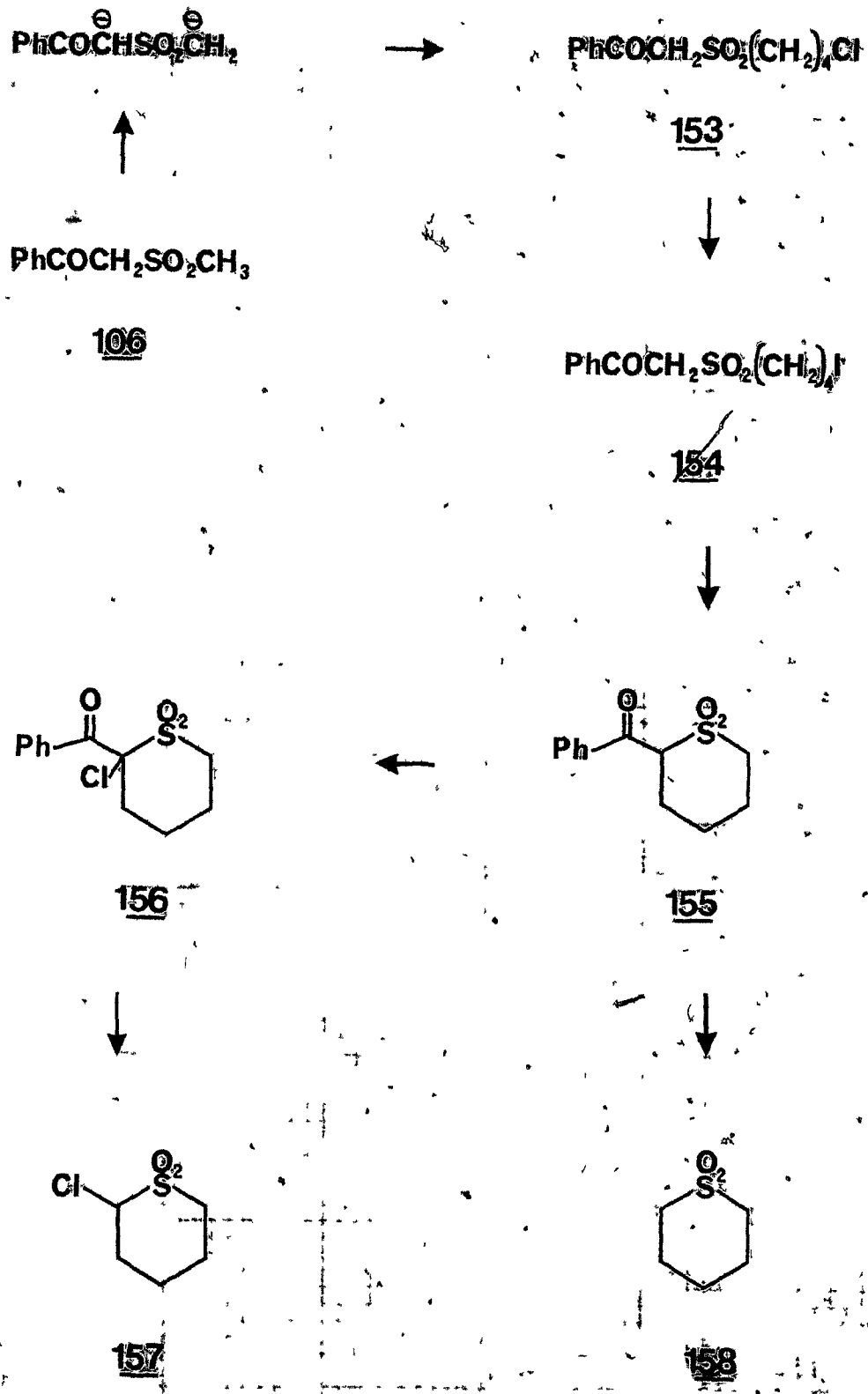
* The author wishes to acknowledge Prof.T.Durst for these samples.

Scheme VI:


PhCOCHSO2CH2
PhCOCH2SO2(CH2)4Cl
153
PhCOCH2SO2CH3
106
PhCOCH2SO2(CH2)4I
154
Ph
Cl
156
155
157
158

conformational studies undertaken.[211] The reported synthesis of such compounds generally start from 1,5-diols which are converted to thianes, in several steps, and these are then oxidised to the corresponding thiane-1,1-dioxides. The overall yields for these multi-step syntheses are generally quite poor and it is not easy to functionalise the different ring positions.[211]

The structures of all the compounds produced in this project were confirmed by the usual combination of spectroscopic methods. However, the complexity of the highly coupled, nine-spin system of the thiane-1,1-dioxide ring protons in **155** and **157** could only be investigated in a meaningful way by the use of a 360 MHz nmr spectrometer which was the highest field strength available. At 360 MHz the signals in the proton nmr spectrum were sufficiently dispersed so as to allow observation, without overlap, of all the proton resonances. The aliphatic region of the proton nmr spectrum of **155** is reproduced in Figure XIII and the details of the aliphatic regions for both **155** and **157** are reported in Tables VII and VIII respectively. These tables include details of a systematic homonuclear decoupling study for each compound. In addition **155** also showed a multiplet in the aromatic region, typical of a benzoyl group.

In both compounds the proton on C-2 was readily

Figure XIII: The aliphatic region of the proton nmr spectrum of **155**

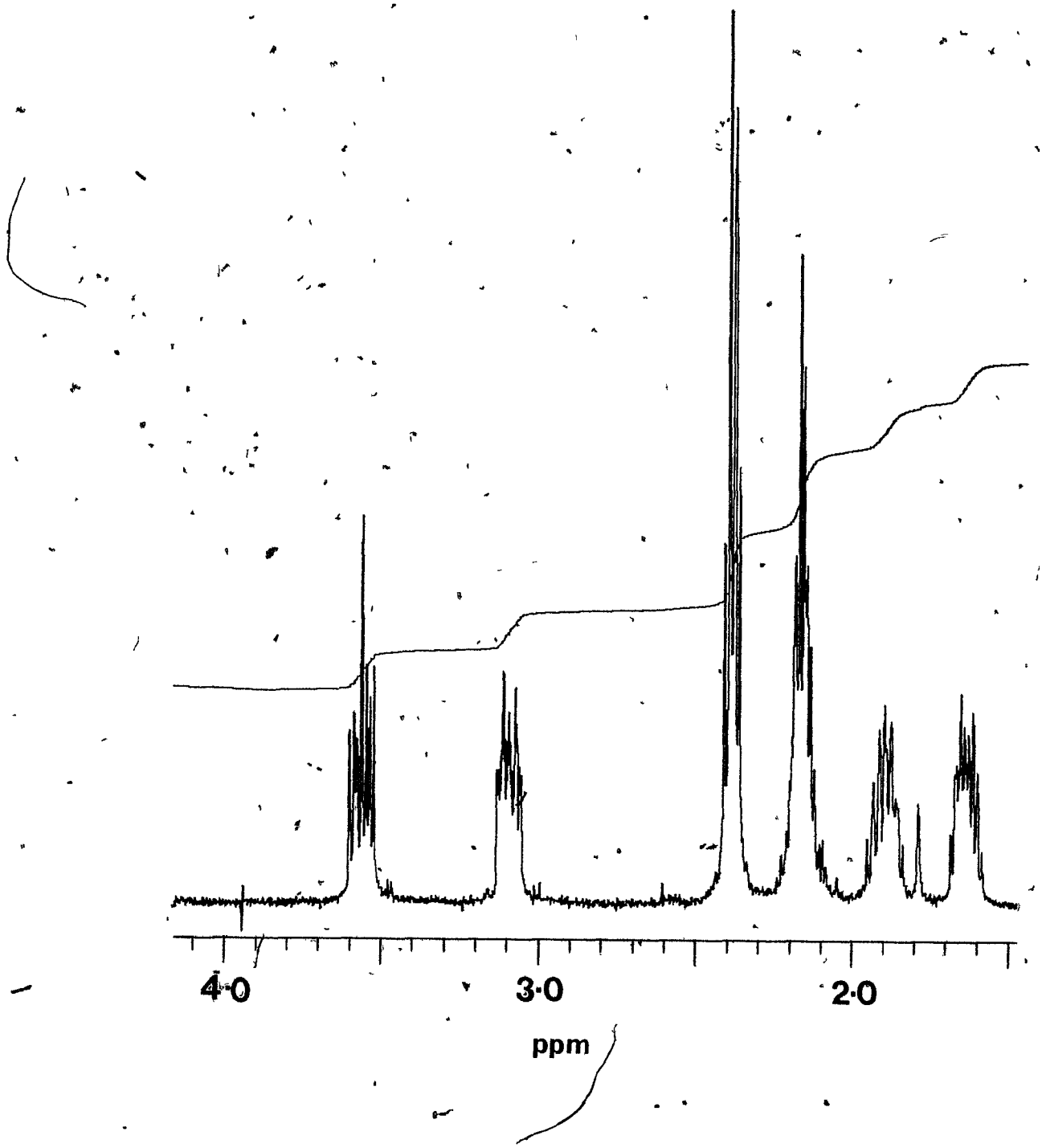


Table VII: ^1H *NMR results for 2-benzoylthiane-1,1-dioxide,155, in* $CDCl_3$ *at 25°C.*

^1H Irradiated \ Observed ^1H	H2	$H6_{ax}$	$H6_{eq}$	H3	H5	$H4_{ax}$	$H4_{eq}$
	4.94	3.55	3.12	2.37	2.11	1.86	1.62
none	dt	ddd	ddt	m	m	m	m
H2	X	no change	dt	simpf m	no change	no change	no change
$H6_{ax}$	no change	X	dt no J_{gem}	no change	simpf m	no change	no change
$H6_{eq}$	t J_{vic}=5.25	dd no J_{gem}	X	no change	simpf m	no change	no change
H3	d ^4J=1.83	no change	no change	X	no change	simpf m	simpf m
H5	no change	d J_{gem}=13.9	dd	no change	X	simpf m	simpf m
$H4_{ax}$	no change	no change	no change	simpf m	simpf m	X	simpf m
$H4_{eq}$	no change	no change	no change	simpf m	simpf m	simpf m	X

Table VIII: ^1H NMR results for 2-chlorothiane-1,1-dioxide, 157, in $CDCl_3$ at 25°C.

^1H Irradiated	Observed ^1H	H2	$H6_{ax}$	$H6_{eq}$	$H3_{ax}$	$H3_{eq}$	H5	$H4_{ax}$	$H4_{eq}$
none		4.73	3.42	2.95	2.60	2.30	2.10	1.93	1.67
		ddd*	ddd	ddt	dddd	ddt	m	m	m
H2		X	no change	dt	simpf m	no change	no change	no change	no change
$H6_{ax}$		no change	X	dt	no change	no change	simpf m	no change	no change
$H6_{eq}$		dd	dd	X	no change	no change	simpf m	no change	no change
$H3_{ax}$		dd	no change	no change	X	dt	no change	simpf m	simpf m
$H3_{eq}$		dd	no change	no change	ddd	X	no change	simpf m	simpf m

* J_{vic} = 3.3 Hz, J_{vic} = 6.6 Hz, ^4J = 2.23 Hz.

assigned as its chemical shift was the furthest downfield in the aliphatic region of the proton nmr spectrum and this provided the starting point for the analysis of the spectra. In addition to the vicinal coupling to the protons on C-3, there is also a long-range doublet splitting caused by coupling with a single proton on C-6. In **155**, the two protons on C-3 interact with H-2 causing the resonance for the hydrogen on C-2 to appear as a doublet of triplets (see Figure XIV). For **157** the two protons on C-3 interact differently and therefore the resonance for H-2 in that compound is a doublet of a doublet of doublets (see Figure XV). Long-range coupling through the sulphone moiety as observed in **155** and **157** has been considered before. In acyclic sulphones such coupling is in the range 0.5-0.8Hz.[18] A much higher coupling constant ($^4J_{eq-eq}$ = 2.3 ± 0.4Hz) has been reported in a more rigid cyclic system[19] whilst in butadiene sulphone the observed coupling constants are $^4J_{trans}$ = 1.265 ± 0.015Hz and $^4J_{cis}$ = 1.940 ± 0.015Hz.[212] For the compounds under consideration in the present study ^4J = 1.85Hz in **155** and ^4J = 2.23Hz in **157**. These data are then good evidence for the proposal that the benzoyl and chloro groups at C-2 in **155** and **157** respectively are predominantly axially oriented. Such a conclusion is drawn from the fact that substantial long-range coupling constants are generally only observed

Figure XIV: Proton nmr resonance of H-2 in **155**

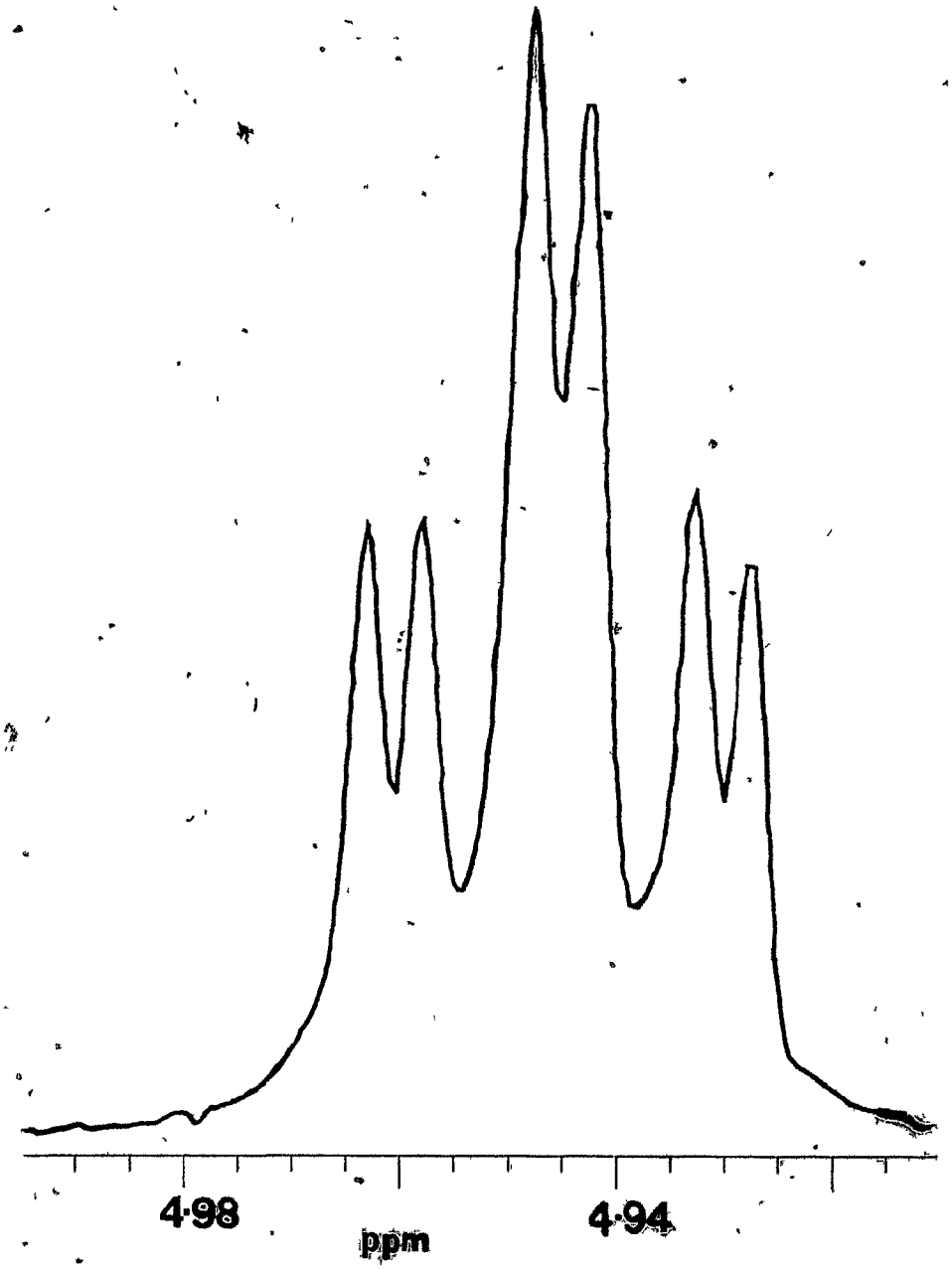
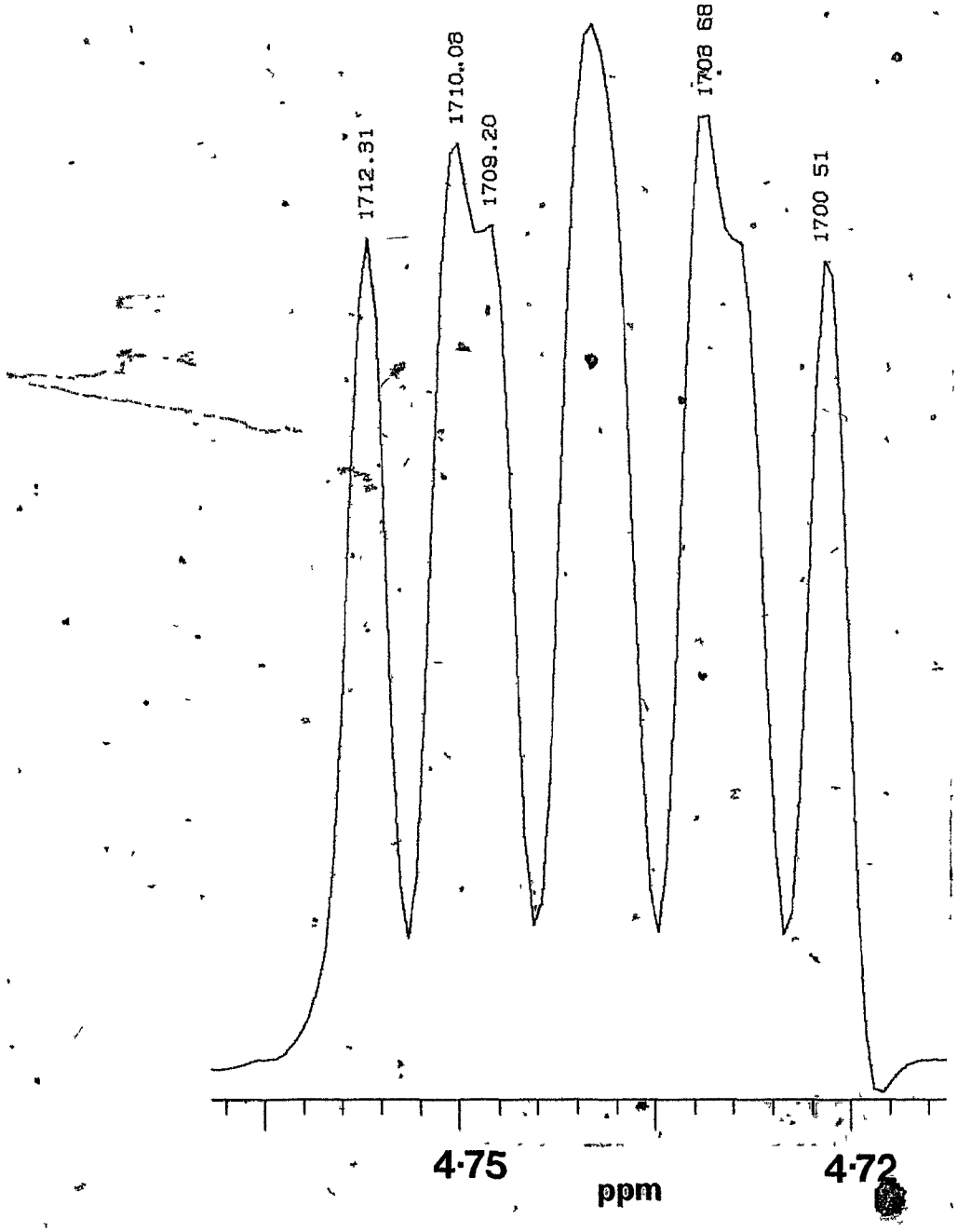


Figure XV: Proton nmr resonance of H-2 in 157



if the protons are aligned in a 'W'- conformation.[213]

The axial proton on C-6 was identified as the member of the protons attached to C-6 which was not affected by irradiation of the proton on C-2. The protons on C-3 and C-5 were assigned according to the results of irradiation experiments and from consideration of the expected chemical shifts of such protons. The only remaining assignments were for the two protons on C-4 which are the lowest frequency proton absorptions in spectra of **155** and **157**. Computer simulations of the protons on C-3 gave satisfactory agreement only if the equatorial proton corresponded with the signal at the lower frequency compared with that for the axial proton. This finding is in contrast to the general results of Lambert and Goldstein[214] who showed that in simple thiane-1,1-dioxides the axial protons resonate at the higher fields when compared with equatorial protons on the same carbon atom.

The structures outlined above are supported by the proton nmr spectra obtained at -65°C. These showed few changes compared with those recorded at ambient temperature, the only differences observed were the broadening of the aromatic resonances in the spectrum of **155** together with concommitant broadening of those at 3.55ppm and 1.86ppm. It is believed that this effect involves the rotation of the benzoyl group which would

influence the axial protons (those protons closest to the group) and hence this finding adds weight to the equatorial proton on C-4 resonating at a higher field than the axial proton.

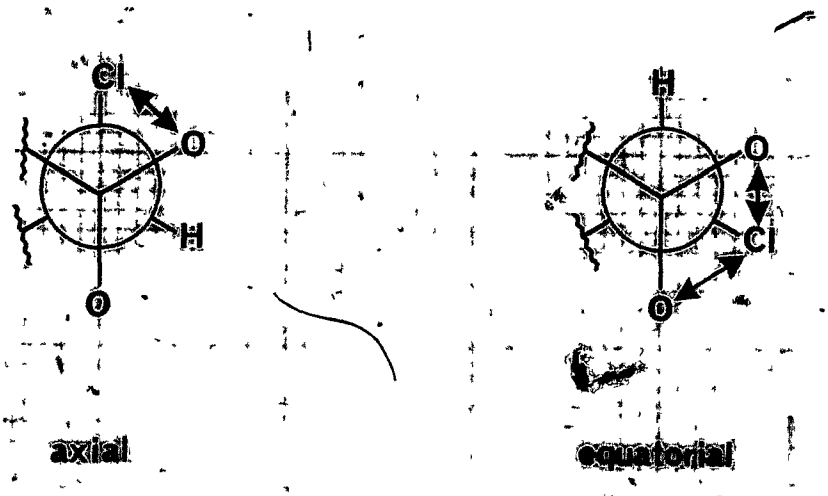
A solution of **155** in d_5-nitrobenzene allowed the observation of separate resonances for the axial and equatorial protons on C-3 at 2.15ppm and 2.05ppm respectively. The rest of the spectrum remained very similar to that that is obtained in $CDCl_3$ solution. On warming the d_5-nitrobenzene solution up to 60°C there was no change in the observed spectrum.

All the above results require that the structures of **155** and **157** are mainly:

155 **157**

i.e. that the equilibrium for an axial versus an equatorial benzoyl or chloro substituent is signific[illegible] biased towards the side of the axial conformer. It is well known that the barrier to ring-

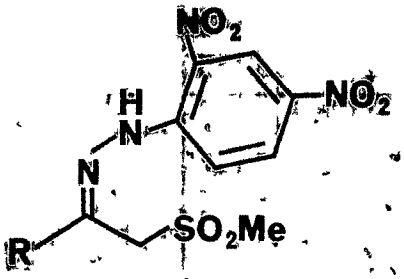
inversion of thiane-1,1-dioxides is similar to that of cyclohexanes[215] and it would be quite extraordinary if this had been affected significantly by the introduction of a benzoyl or a chloro group in the 2-position. From the results of this work it is proposed that in **155** and **157** the conformational effects observed result from an energy difference of at least 12kJmol^{-1} between the axially and equatorially substituted rings. This difference is, in part, because of the non-bonding interactions within the molecule. A polar, axial substituent such as chloro will have <u>one</u> unfavourable <u>gauche</u> interaction with one of the polar sulphone oxygen bonds and this is apparently preferable to <u>two</u> such interactions in the case of an equatorial chloro substituent. In acyclic sulphones the former type of orientation appears to be the most favoured both in the solid state and in solution.[73, 216, 217, 218]



The carbon-13 nmr data of compounds **155** and **157** confirms their structure and from these data the γ-gauche effects of a benzoyl and a chloro group across a sulphone in a thiane-1,1-dioxide ring system were found to be -0.2ppm and -4.2ppm respectively. As far as the author is aware there are no data available at present with which to compare these figures.

Reactions of the carbonyl group of β-ketosulphones and some of their derivatives.

The β-ketosulphones **106** and **128** reacted with 2,4-dinitrophenylhydrazine to form the corresponding hydrazones **159** and **160** using the usual reagents[219] as for regular ketones. The proton nmr spectra of these

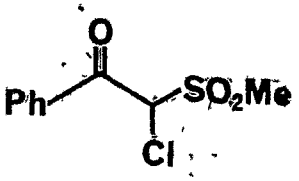


159 R = Ph

160 R = Et

compounds agreed with the expected structures. However, no such hydrazones have been obtained for the mono or bissulphenylated β-ketosulphones nor for the oxidised

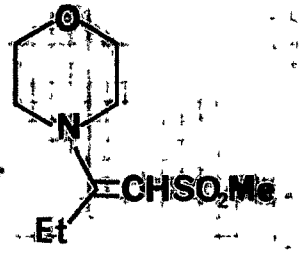
monosulphenylated compounds. Attempted hydrazone formation using the α-chloro-β-ketosulphone, **112** resulted in the formation of hydrazone **159** i.e. the



112

chlorine atom was reduced. Attempts to prepare the hydrazones of the long-chain containing β-ketosulphones, **130**, have all failed but this could be due to solubility problems with the starting β-ketosulphones.

1-Methylsulphonylbutan-2-one, **128**, reacted with morpholine on azeotropic removal of water to form a mixture of *cis* and *trans* isomers of the enamine **161**. The



161

proton nmr spectrum of the mixture is very complex and it has not been possible to isolate either isomer in a

pure state. Attempts to react the monosulphenylated compound, **129** or its oxidation product, **134**, have failed.

The above data suggest that the ketone in a simple β-ketosulphone is similar, in terms of reactivity, to a simple ketone whilst in monosulphenylated derivatives and their oxidation products this is not so. The reactivity of the keto group in these latter compounds is much reduced, this marked effect is due to a combination of the electronic and steric effects of the extra substituents on the α-carbon atom. These attached groups are all electron-withdrawing in nature and further work is required in this area in order to determine which parameters are important.

pK_a values of some β-ketosulphones and their derivatives.

The pK_a values of nineteen β-ketosulphones and derivatives were measured in the present study. Several other compounds were also investigated as discussed below. All the results obtained are presented in Table IX. The tabulated pK_a values are the average of three measurements wherever possible and the estimated error in these results is ± 0.1 pK_a units.

The pK_a values were measured in 50% ethanol - 50% water solutions which were typically 0.01 - 0.02M with

Table IX: Experimentally determined pKa values is 50:50 ethanol-water at 30°C.

Compound:	#	pKa(±0.1)*	comments.
$PhCOCH_2SO_2Me$	**106**	9.80	not dried
		10.53	
$PhCOCH(Cl)SO_2Me$	**112**	9.26	drifted near end point
$PhCOCH(Br)SO_2Me$	**113**	9.66	drifted near end point
$PhCOCH(SMe)SO_2Me$	**162**	9.04	
$PhCOCH(SEt)SO_2Me$	**114**	8.96	
$PhCOCH(SPh)SO_2Me$	**144**	6.95	
$PhCOCH(SO_2Me)SO_2Me$	**163**	4.16	
$PhCOCH(SO_2Ph)SO_2Me$	**164**	4.28	
$PhCOCH(Me)SO_2Me$	**165**	-	too weakly acidic to measure
$PhCOCH_2SO_2Ph$	**166**	10.50	
$PhCOCH(SMe)SO_2Ph$	**167**	9.05	
$PhCOCH(SEt)SO_2Ph$	**168**	8.97	
$PhCOCH(SPh)SO_2Ph$	**169**	7.16	

Table IX: (cont.)

Compounds	#	pKa(±0.1)*	comments.
$MeCOCH_2SO_2Ph$	**170**	10.65	
$MeCOCH(SMe)SO_2Ph$	**171**	9.15	only one titration
$MeCOCH(SPh)SO_2Ph$	**172**	7.05	only one titration
$EtCOCH_2SO_2Me$	**128**	11.34	
$Me(CH_2)_{10}COCH_2SO_2Me$	**173**	11.26	
$Me(CH_2)_{12}COCH_2SO_2Me$	**174**	11.59	
$Me(CH_2)_{14}COCH_2SO_2Me$	**175**	-	not soluble enough
$Me(CH_2)_{12}COCH(SMe)SO_2Me$	**176**	9.37	
$Et_3N^+HCl^-$		10.18	
$MeCOCH_2COMe$		9.84	
$pCl\text{-}C_6H_4OH$		11.11	

*Except for those values resulting from only one titration.

respect to the acid. These solutions were flushed with nitrogen prior to measurements being made at 30 ± 1°C in a large thermostatically controlled bath. A glass electrode was used to measure the pH of the acid-containing solution, whilst a standardised tetramethylammonium hydroxide solution (approximately 0.8M) was added in measured amounts using a micro-burette. Measurements were carried out as quickly as possible in order to alleviate problems of hydrolysis which occured for some of the compounds.

It is most preferable to use purely aqueous solutions when using a glass electrode to measure the pH. However, since most of the compounds considered here are not soluble in water the solvent of choice, 50:50 ethanol - water allowed pK_a values to be measured in a medium with a fairly high dielectric constant which would be compatible with the application of these compounds as anti-bacterial and other agents as described above. In such applications a knowledge of the pK_a values of these compounds may be useful when assessing their activities.

Several groups of workers have used glass combination electrodes to measure the pH of ethanol - water solutions and have encountered few difficulties with solutions containing less than seventy-five weight percent ethanol.[156] Moreover, Beck and Wynne-Jones[220]

have shown that such an electrode shows good stability with time and the results obtained are reproducible.

It should be noted that in general the pK_a value for acids is raised by about one unit (i.e. they become less acidic) in 50% ethanol - 50% water compared with a purely aqueous solution.[158] A word of caution should also be introduced; comparison of the pK_a values of several compounds in a series in a given solvent system is acceptable, but comparison of the same compounds in a series of different solvents may not lead to meaningful results.[158]

pK_a values may be obtained by several different methods using the titration results obtained. The two most common methods are now described. Since pK_a is related to pH by the following equation:

$$pK_a = pH + \log [HA] / [A^-]$$

it follows that at the half-neutral isolation point, when $[HA] = [A^-]$ the pK_a value of the compound being investigated will be equivalent to the measured pH of the solution. The half-neutralisation point may be obtained from a plot of pH *versus* volume of base added or preferably from a plot of $1/\Delta$ pH *versus* volume of base added (a Gran plot). The results for **167** are reproduced in the Experimental section as an example of

$PhCOCHSO_2Ph$
|
SMe .

167

how this method was used and for comparison with the more accurate method described below. The pK_a value obtained by this method is an approximation. However, it is often used since it is easily obtained and is useful for rapid comparison of pK_a results.

Albert and Serjeant[158] have decried the above commonly used method for the calculation of pK_a values from experimental data. Instead they have suggested that the average of several calculated pK_a values at different extents of neutralisation, before the end-point, could be calculated. Since any titration results which result in pH readings more basic than 10 (all the ones in the current work did) require correction for hydroxyl ion concentrations[158] the equation used to obtain pK_a values in this study was as follows:

$$pK_a = pH + \log ([HA] + [OH^-] \ / \ [A^-] - [OH^-])$$

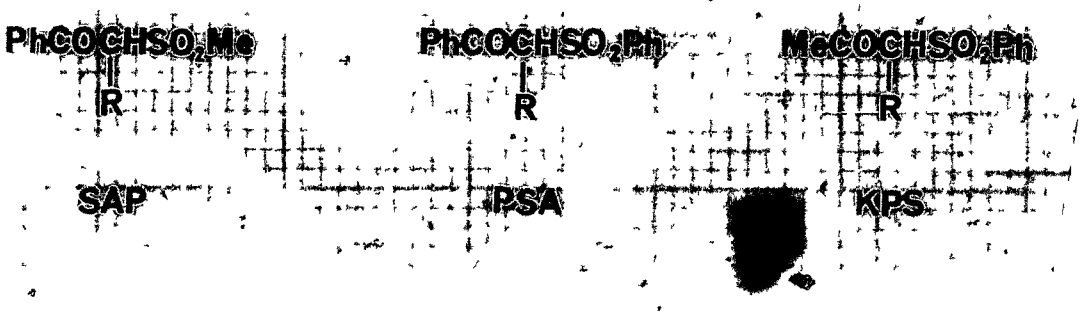
Table V, page 110, lists all the published pK_a values of β-ketosulphones to-date. In the present study the first three compounds in this table have been

reinvestigated and the results obtained are at variance with those reported.[187] One possible explanation for this difference is that the earlier workers may not have dried their compounds thoroughly. In the current study compounds were routinely dried, using a drying pistol, for two hours *in vacuo* immediately prior to measurement of pK_a values. A sample of 2-methylsulphonyl-1-phenylethanone, **106**, which had been prepared some months previously, gave a pK_a of 9.80 ± 0.1 when it was not dried *in vacuo*. This result is close to the value of 10.01 ± 0.02 obtained by Truce *et al.*[187] and tends to lend credence to the above explanation.

Since these results were different from those already reported in the literature, the pK_a values of several compounds which are readily available and easily purified were measured. The pK_a values for these compounds are given in Table VIII, unfortunately there are no literature values for these compounds in the present solvent system. They were chosen as benchmarks by which other workers may compare these results. The pH electrode was standardised with standard buffers before and after doing a titration and the results obtained were discarded if the pH of these was not as stated in the literature (see Experimental section for more details).

As was discussed in the introduction to this project

(Chapter 4), the pK_a values for various series of carbon acids with substituents directly attached to the carbon atom bearing the ionising proton, have been investigated.[169-171,179,180,182,185,186] One group [171,173] have obtained a linear correlation of their pK_a results for substituted dinitroalkanes with the Taft σ^* parameter. The other sets of parameters have all been correlated in a similar manner by the author, using σ^* values generally available in the literature.[183] These correlations were shown in the introduction for completeness and are now all presented in Table X. This table also shows the correlation of the pK_a results obtained in the present study for three different series of substituted β-ketosulphones with σ^*. These series have been named the SAP,PSA and KPS series respectively and the parent compound of each of these series respectively is shown below, in this case R=H. Other



correlations relating the pK_a values of these compounds with different σ parameters and with group electronegativities[221] did not produce useful results.

Table X: Correlations of the pK_a values of some carbon acids with σ^*.

Series:	linear relationship	correlation coefficient	no. of compounds
$(NO_2)_2CHR$	$pKa = 5.23 - 3.29\ \sigma^*$	-	81†
$(MeCO)_2CHR$	$pKa = 10.53 - 1.62\ \sigma^*$	0.977	6†
$MeCOCH(R)CO_2Et$	$pKa = 12.57 - 3.21\ \sigma^*$	0.979	5†
$(EtSO_2)_2CHR$	$pKa = 2.55 - 0.65\ \sigma^*$	0.999	3†
$(PhCH_2SO_2)_2CHR$	$pKa = 14.48 - 5.11\ \sigma^*$	0.979	4†
$PhCOCH(R)SO_2Me$ (SAP)	$pKa = 11.84 - 2.19\ \sigma^*$	0.976	6
$PhCOCH(R)SO_2Ph$ (PSA)	$pKa = 11.71 - 2.04\ \sigma^*$	0.901	4
$MeCOCH(R)SO_2Ph$ (KPS)	$pKa = 11.95 - 2.30\ \sigma^*$	0.920	3

†These correlations have been calculated from literature data; see p. 106, et seq.

The correlation for the SAP series does not include the data for the bromo and chloro derivatives since inspection of the graph of pK_a *versus* σ^* indicates that the data points for these compounds fall well off the line. This graph is presented as Figure XVI. It should be noted that the correlation presented for the series of substituted acetylacetones is significantly worsened if the datum for the bromo compound reported by Schwarzenbach and Felder[179] is included. These workers reported that this compound gave an inaccurate pK_a value since it was readily hydrolysed. In the present work it was found that **112** and **113** in the SAP series also show

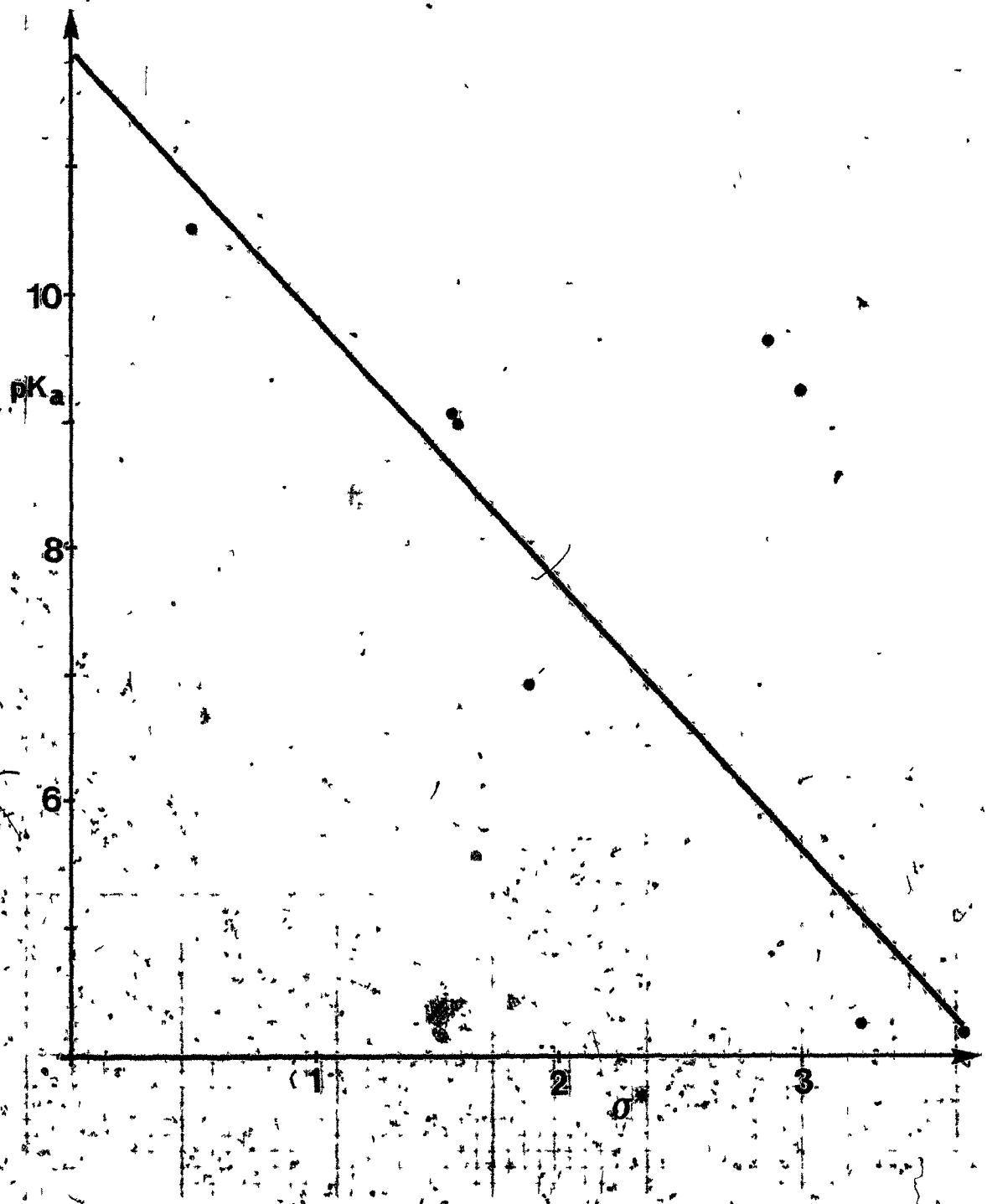
112 X = Cl

113 X = Br

signs of hydrolysis since the pH readings obtained tended to be unstable and drifted around the end-point of the titration. This hydrolysis has also been observed, and used synthetically by Grossert *et al.*[73] and by the present author (**156** → **157**).

Barlin and Perrin[174] have indicated that all correlations of pK_a values of carbon acids with σ^*

Figure XVI: pK_a values of β-ketosulphones in the SAP series versus σ^*.



should exhibit a slope of 3.5 ± 0.4 and have cited results for substituted ethylacetoacetates to support this. This value for the slope was obtained from consideration of several other systems where the substituent is directly attached to the atom possessing the ionising proton. Such systems include RNH_3^+,[183] RSH[183] and ROH[222] where the slopes are 3.14, 3.50 and 3.9 respectively. Inspection of Table X will convince the reader that this generalisation is not correct i.e. only two of the eight correlations presented in the table fit within the suggested limits. Of these two the substituted dinitromethane series are not good examples of carbon acids (see note above) and the other correlation may just have a slope in the 'expected' range by chance. The conjugate bases from ionisation of RSH and ROH involve atoms that can readily hold a negative charge and the conjugate base of RNH_3^+ is neutral; these are very different from a carbon acid where the carbon atom is unable to hold a charge so readily. Thus it would be expected that C-H acids should be different from the other series and hence perhaps the slope should not be in the range quoted above as is indeed the case.

The σ^* values derived by Taft reflect the polar character of a substituent attached directly to the reaction centre of a molecule. These values were

calculated using the hydrolysis of esters as the reference reaction and the steric influences of the substituents have been removed from the constant. There has been much discussion concerning the validity of σ^* as a purely polar parameter[223] and an alternative polar parameter σ_I has been proposed. Use of this parameter for correlation of the data for acetylacetones gives a worse correlation. Unfortunately, relatively few σ_I parameters are available and thus a correlation with the pK_a values obtained in the present study was not possible.

The slopes of the correlations given in Table X indicate a measure of the sensitivity of the series of compounds, under consideration, to the polar effects of their substituents. The variations in these slopes from -0.65 to -5.11 are not readily explained in terms of the gross structure of the molecules being considered. All the β-ketosulphone correlations show similar slopes (-2.04, -2.19 and -2.30) which would be expected since the compounds have very similar structures. It is however, rather suprising that the diethylsulphonylmethane and dibenzylsulphonylmethane correlations have such different slopes (-0.65 and -5.11 respectively) since the parent compounds differ only by the exchange of a methyl group for a phenyl group in the α-position relative to the ionising proton.

In addition to those β-ketosulphone derivatives in the SAP, PSA and KPS series which have been discussed above the pK_a values of five other β-ketosulphone derived species have been measured. The long-chain β-ketosulphones, **130**, themselves show pK_a values of 11.34, 11.26 and 11.59, that is, they are weaker acids than is **106** ($PhCOCH_2SO_2Me$). This would be expected since the benzoyl group in **106** is more able to stabilise the negative charge developed on ionisation compared with an alkylcarbonyl substituent in **130**. This ability is quantified by the σ^* values for these groups which are 2.2 *vs* 1.81 respectively.[183]

The monosulphenylated myristyl-derived β-ketosulphone in the table showed a pK_a which is 2.22 units more acidic than the parent β-ketosulphone itself. This compares with the acidity enhancing effect of the α-methylthio group of 1.49, 1.45 and 1.50 pK_a units respectively in the SAP, PSA and KPS series. The β-ketosulphone with the palmityl chain was too insoluble for an accurate pK_a value to be measured.

Thus, the pK_a results from the three series of compounds (SAP, PSA and KPS) are self-consistent but it is difficult to draw meaningful comparisons with other series of compounds due to the paucity of published results on compounds that can reasonably be directly compared.

Summary

In this part of the present work a new series of β-ketosulphones and some sulphenylated derivatives and their oxidation products have been prepared and identified.

A new facile, high-yield synthesis of substituted thiane-1,1-dioxides has been presented via the alkylation of a dianion of a β-ketosulphone. It has been shown by an extensive proton nmr study that 2-chloro and 2-benzoyl thiane-1,1-dioxides exist in $CDCl_3$ solution primarily with the 2-substituent in the axial orientation. Such a conformational preference arising from polar rather than steric forces in cyclic sulphones is quite unusual.

The carbonyl group in a β-ketosulphone shows reactivity like that of a simple ketone since it reacts to form hydrazones and enamines. The similar group in the monosulphenylated β-ketosulphones and their oxidation products does not undergo such reactions.

The pK_a values of nineteen β-ketosulphones have been measured and these have been correlated with σ^* as have other carbon acid data available in the literature.

Suggestions for further work

Probably the most important project to stem from the current study will be an investigation of the properties

of the compounds prepared here. As has been mentioned above, such compounds may have useful anti-bacterial and other properties and they may also be good detergents. Since there are several large industrial concerns that are willing to test compounds like these in order to determine their usefulness as agrochemicals etc. this project is probably best left to these companies. A selection of these compounds have been submitted for study of their action against Dutch elm disease however, no results have been reported so far.

The reactions of the keto group in the compounds of interest are part of an ongoing group project, an honours student is investigating the preparation and reactions of ketals and oximes of β-ketosulphones.

The facile, high-yield preparation of thiane-1,1-dioxides described above should prove adaptable to other similar compounds. Once made, these compounds could be subjected to the same spectroscopic analysis in order to determine their conformations in solution.

It would be interesting to investigate the oxygen-17 nmr spectra of 2-substituted-thiane-1,1-dioxides since if the substituent is preferentially axial, the environment around the sulphone oxygen atoms will be different and so two resonances would be expected in the spectrum.

The measurement of the pK_a values of the compounds prepared in this project has raised many unanswered questions, the major one being, what is the significance of the slope of the line from the correlation with σ^*? Further studies are required in order to answer this question, for example. other series of 1,3-diketones should be investigated to see whether the slopes for these are similar to the acetylacetone results. Some of the presented correlations have only a few data points and the substituents used exhibit a narrow range of σ^* values. Such ranges should be extended so that better correlating may be obtained.

PART III

NUCLEAR MAGNETIC RESONANCE OF THE SULPHUR-33 NUCLEUS IN SULPHONES

CHAPTER 6

INTRODUCTION - SULPHUR-33 NMR

The first successful nuclear magnetic resonance experiments were carried out by physicists but the technique has been especially nurtured by chemists. New applications of this type of spectroscopy continue to be recorded in many fields of science. In this chapter sulphur-33 nuclear magnetic resonance will be reviewed in the perspective of the whole field of nmr spectroscopy, followed by a comprehensive review of the sulphur-33 nmr literature.

Historical

The first successful experiments in the field of nuclear magnetic resonance spectroscopy were completed in late 1945 by Bloch *et al.*[224] at Stanford and by Purcell *et al.*[225] at MIT. These scientists obtained proton nmr signals from water and solid parafin wax respectively; thus a new technique for the determination of molecular structure was born. This major achievement was acknowledged by the award of the 1952 Nobel prize for physics to Bloch and Purcell.

During the late 1940's and early 1950's there were many reports concerning the observation of nmr signals from various nuclei. These included some metals,[226]

nitrogen-14,[227] fluorine-19[228] and sulphur-33 in carbon disulphide.[229] Of these the work of Dickinson[228] concerning fluorine-19 is the most notable since he introduced two concepts vital to modern nuclear magnetic resonance spectroscopy. Firstly he reported the 'most unexpected' observation that fluorine atoms in different environments showed different resonance positions; thus the concept of chemical shift was introduced. Dickinson[228] also attempted, in vain, to obtain similar results from proton nmr measurements. He reported that within the accuracy of the experiments (5 parts in a million) the resonances of acetone, Nujol, distilled water, glacial acetic acid, glycerin and anhydrous diethyl ether were coincident. Secondly, Dickinson used the fluorine-19 resonance of BeF_2 as a standard with which to compare the resonances of other compounds; thus the idea of a nmr reference standard was introduced.

In 1951 the now classical work of Arnold, Dharmatti and Packard[230] showed that the proton nuclear magnetic resonance spectrum of ethanol exhibited three peaks corresponding to the three different types of protons present in the molecule; this spectrum is reproduced in Figure XVII. This result was a significant breakthrough and caused a great flurry of activity in the area of proton nuclear magnetic resonance spectroscopy which eventually led to the establishment of this technique as

Figure XVII: The first proton nmr spectrum showing resolution of protons in different chemical environments.

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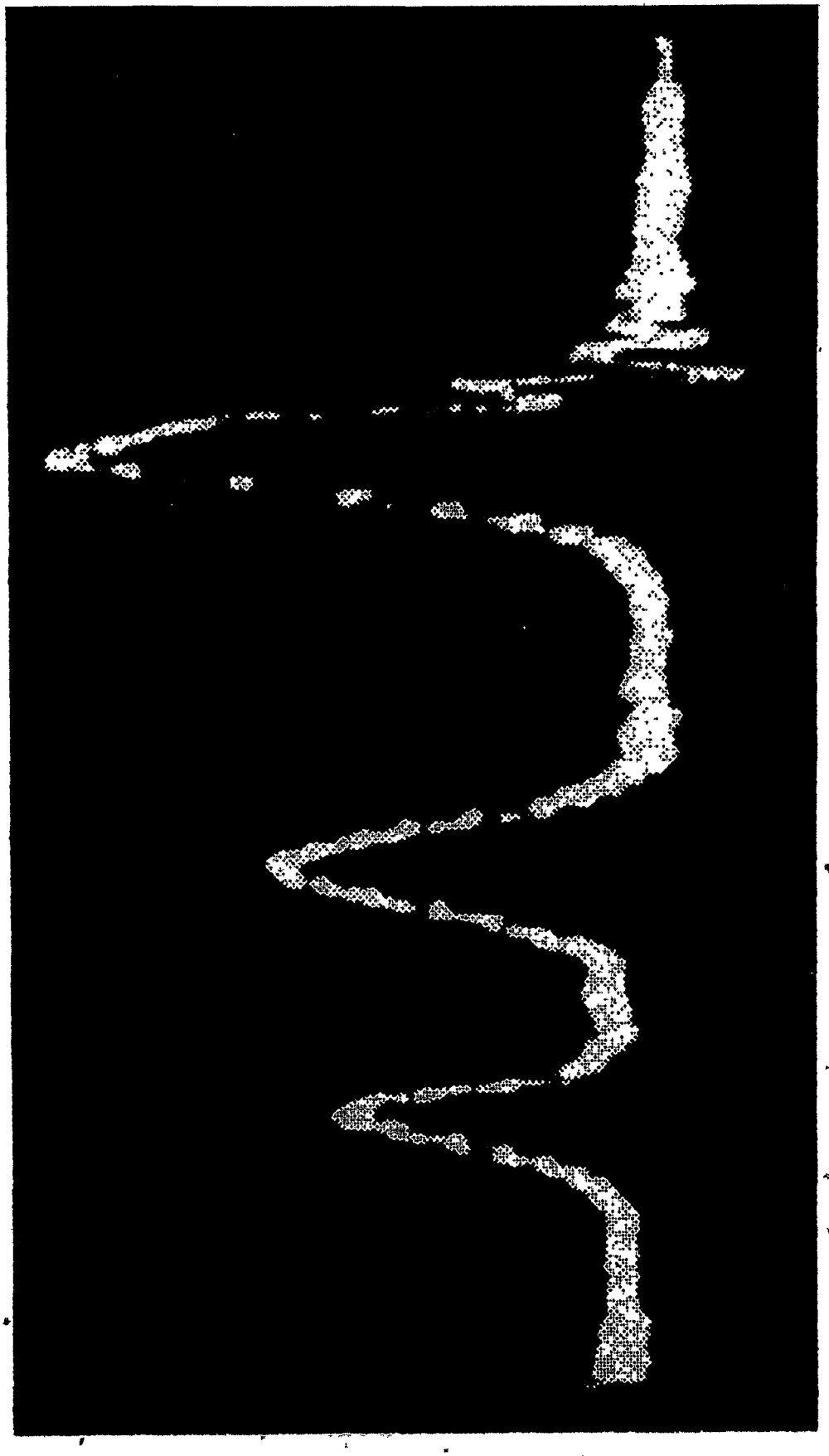


a routine analytical method for the determination of the structures of organic compounds amongst other things.

All of these early nmr measurements were made using continuous-wave instruments (CW) with one of the magnetic field or the radio frequency emitter fixed and the other variable. This type of equipment allowed only a few nmr active nuclei (^{1}H, ^{19}F, ^{31}P and ^{13}C) to be studied in any depth. The advent of the commercial Fourier-transform nmr spectrophotometer around 1970 broadened the scope of nmr measurements so that at present there are as many as ninety nuclei that have been investigated to some degree. Harris and Mann[231] have edited an excellent volume which deals with many of these nuclei and this has recently been updated by work of Laszlo.[232] The reader is directed to these works for much excellent information; the present report concentrates on the nuclear magnetic resonance studies of sulphur and to a lesser extent its Group VI relatives.

Nuclear magnetic resonance of Group VI nuclei.

Many organic compounds contain oxygen and to a lesser extent sulphur and it is perhaps somewhat fortuitous that the major isotopes of these Group VI elements i.e. ^{16}O, ^{32}S and ^{34}S possess nuclear spin quantum numbers of zero. If it was not for this lack of

nmr activity, the appearance of many proton and other nmr spectra would be quite inconveniently complex due to the coupling effects of these nuclei.

Table XI lists the twenty-one isotopes of the Group VI elements which possess a significant natural abundance. Nuclear spin quantum numbers (I) and receptivities relative to carbon-13 are presented where appropriate. It can be seen from this table that only eight of these isotopes have non-zero nuclear spin quantum numbers and are hence nmr active. No isotopes of polonium are presented in the table since there are none of significant abundance; this element will thus not be considered. Due to the fact that oxygen is the most abundant element in the Earth's crust[236] and hence occurs widely in both inorganic and organic compounds, oxygen-17 nmr has been studied in great detail. This is despite the fact that oxygen-17 is much less receptive than is carbon-13 and that it has a quadrupolar moment which leads to broad lines, even in the case of small molecules. Oxygen-17 studies have been greatly assisted by the fact that it is a relatively cheap isotope and is easily introduced into the desired molecules. The reader is referred to the excellent reviews of Rodger et al.,[237] Kintzinger[238,239] and Klemperer[240] for more information concerning oxygen-17 nmr.

Of the selenium isotopes listed in Table XI only

Table XI: Isotopes of the Group VI elements.

Isotope	Nuclear spin[233] Quantum number	Natural[234] Abundance	Receptivity*[235]
^{16}O	0	99.759	
^{17}O	5/2	0.037	6.11×10^{-2}
^{18}O	0	0.204	
^{32}S	0	95.0	
^{33}S	3/2	0.76	9.73×10^{-2}
^{34}S	0	4.22	
^{36}S	0	0.014	
^{74}Se	0	0.87	
^{76}Se	0	9.02	
^{77}Se	1/2	7.58	2.98
^{78}Se	0	23.52	
^{80}Se	0	49.82	
^{82}Se	0	9.19	
^{120}Te	2	0.089	+
^{122}Te	2	2.46	+
^{123}Te	1/2	0.87	0.89
^{124}Te	2	4.61	+
^{125}Te	1/2	6.99	12.5
^{126}Te	0	18.71	
^{128}Te	0	31.79	
^{130}Te	0	34.48	

* This is a measure of the ease with which an nmr spectrum can be obtained relative to carbon-13.
\+ Not available.

selenium-77 has a non-zero nuclear spin quantum number. Its receptivity is greater than that of carbon-13 and since I=1/2, selenium-77 is a good candidate for study by nmr. More than 150 chemical shifts have been reported for this nucleus and interest is certain to be maintained owing to the central position of selenium in the semiconductor industry.

Tellurium has five nmr-active nuclei, but nuclear magnetic resonance measurements have only been reported for tellurium-123 and tellurium-125. As shown in Table XI, tellurium-120, tellurium-122 and tellurium-124 have nuclear quadrupolar moments (spin quantum numbers of 2). These isotopes are also relatively scarce and hence no nmr measurements have been reported to date. Owing to its higher natural abundance, tellurium-125 is the more studied of the two nuclei having I=1/2. Over forty chemical shifts have been reported for this nucleus and work continues in this area.

Of the four sulphur isotopes listed in Table XI only sulphur-33 is nmr active. The next section reviews the sulphur-33 nmr literature to date.

Sulphur-33 nuclear magnetic resonance spectroscopy.

As has been mentioned, sulphur-33 was one of the first nuclei studied by nmr;[229] however, this study consisted only of a relatively inaccurate measurement of

the nuclear magnetic moment of sulphur-33 in carbon disulphide relative to nitrogen-14 in nitric acid. A cursory glance at the volumes by Harris and Mann[231] and Laszlo[230] as well as the Specialist Reports on nmr from the Royal Society of Chemistry[241] will convince the reader that sulphur-33 nmr is the least studied amongst the Group VI elements.

It can be seen from Table XI that sulphur-33 is more receptive than oxygen-17 which would tend to suggest that sulphur-33 signals should be more easily obtained. This is not the case and raises the question of how useful the term receptivity is. For nuclei with I=1/2 this term is very useful since it indicates the relative ease of obtaining an nmr spectrum for a particular nucleus. In the case of a nucleus with I > 1/2, however, there are other factors which affect the problem, most notably the ability of a nucleus to relax by quadrupolar mechanisms. Another more useful term, detectability, has been alluded to by Brevard.[242] This term takes into account several other factors not considered in the term receptivity; however, to-date little has been reported in this area.

The first chemical applications of sulphur-33 nuclear magnetic resonance appeared in 1968. In this year Karr and Schultz[243] reported signals for two-sulphide minerals, 1,2-ethanedithiol and elemental

sulphur. The result for elemental sulphur disolved in carbon disulphide has never been reproduced by later workers. Lee[244] measured the temperature dependence of the sulphur-33 nuclear magnetic resonance signal of α-MnS. Five other papers have been published mainly concerning the sulphur-33 nmr of inorganic species (Lutz et al.,[245] Vold et al.,[246] Ancian and co-workers,[247] Kroneck et al.,[248] and Wasylishen et al.[249]).

The first application of sulphur-33 nuclear magnetic resonance to an organic chemistry problem was reported by Retcofsky and Friedel.[250,251] The aim of this work was to use sulphur-33 nmr as an analytical probe for characterising coal and oil samples, since sulphur is an important constituent of these materials. Twelve sulphur-33 chemical shifts were reported relative to carbon disulphide; these data are presented in Table XII. Typically the spectra were obtained in 8-12 hours using a Varian DP-60 spectrometer operating at 4.33 MHz. Retcofsky and Friedel found that only species where the sulphur nucleus had a reasonably symmetrical electric field gradient or a rapidly exchanging system gave useful sulphur-33 nmr signals.

Schultz et al.[252] measured the sulphur-33 nmr spectra of five compounds using pulsed nmr but they did not report chemical shifts. Lutz et al.[253] published a paper which recommended the use of a sulphate salt

Table XII: Chemical shifts after Retcofsky and Friedel.[251]

Compound:	Chemical Shift (ppm)	Approximate Linewidths (Hz)
CS_2	0	180
Thiophene	-220 ± 6	700
Tetrahydrothiophene	89 ± 38	2900
3-Bromothiophene	-134	1800
2-Methylthiophene	-178 ± 9	1400
3-Methylthiophene	-197 ± 26	1800
Ethyldisulphide	168 ± 88	5800
Dimethylsulphoxide	-233 ± 20	2900
Sodium sulphide	261	1800
Sphalerite	230 ± 6	70
Sulphuric acid conc	-225 ± 32	2500
Sulphuric acid 5M	-319 ± 5	1800

dissolved in water as the standard for sulphur-33 chemical shifts due to a much narrower linewidth than that of carbon disulphide. Unfortunately they have not apparently pursued this matter since the publication.

The work reported thus far indicated that the major requirements for the observation of sulphur-33 nmr signals is as symmetrical as possible an electric field gradient around the nucleus. It is thus suprising that the sulphone moiety was not investigated prior to 1981. In this year Faure and co-workers[254] published sulphur-33 spectral parameters for eleven sulphones and four other compounds. These data were obtained using a Varian FT-80 spectrometer and the figures are reproduced in Table XIII. The authors chose these compounds since they are the likely products from the oxidation of the sulphur containing fraction of crude oil samples! The relatively narrow linewidths (50-150Hz) observed in this study are due to the fact that the electric field gradient around the sulphur nucleus is now quite symmetrical. Linewidths increased with increasing substitution which thus seemed to decrease the symmetry of the electric field gradient around the sulphur nucleus. It was noted by the authors that phenyl and vinyl sulphones show resonances upfield relative to alkyl sulphones due to shielding caused by the conjugation of the sulphur atom with the attached group.

Table XIII: Sulphur-33 nmr data after Faure et al.[254]

Compound	δ(ppm)*	Linewidth(Hz)
Thiolane-1,1-dioxide	42±1.5	50
3-Methylthiolane-1,1-dioxide	37±1.5	60
3-Aminothiolane-1,1-dioxide	33±1.5	80
3-Hydroxythiolane-1,1-dioxide	36±1.5	100
2,4-Dimethylthiolane-1,1-dioxide	37±1.5	90
Butadienesulphone	32±1.5	50
$(CH_2=CH)_2SO_2$	-26±1.5	60
Ph_2SO_2	-23±2.0	130
Me_2SO_2	-7±1.5	50
nPr_2SO_2	7±2.0	130
$PhSO_2Me$	-20±2.0	120
$MeSO_3H$	-5±2.5	150
$pCH_3-C_6H_4SO_3H$	-10±1.5	90
$NH_2CH(CO_2H)CH_2SO_3H$	-9±1.5	80
$CH_2=CHSO_3^-Na^+$	-11±1.5	70

* Relative to Sulphur-33 signal of SO_4^{2-} in saturated $(NH_4)_2SO_4$ in D_2O.

Harris and Evans[255] have published the most comprehensive list of sulphur-33 chemical shifts to date. Using a Bruker WM-250 FT nmr instrument they measured the chemical shifts of twenty different organic sulphur-containing compounds; the data are reproduced in Table XIV. Unfortunately these workers chose to report the chemical shift values relative to carbon disulphide and they did not even refer to the work concerning sulphates as standards[253] mentioned above.

It can be seen from the data in Table XIV, and the authors indicated the fact, that lengthening the chains attached to the sulphone group has little effect on the chemical shift of the sulphur nucleus. There is however a ' β-methyl effect' of about 7-8 ppm per methyl group as can be seen from the data. These data also confirm the results of Faure et al.[254] that aryl sulphones show resonances upfield compared with alkyl sulphones.

In a much less widely published report, Annunziata and Barbarella[256] have reported sulphur-33 nuclear magnetic resonance data obtained using a 300 MHz nmr instrument (the data are reproduced in Table XV). Although they were able to obtain sharp lines for simple sulphones, sulphoximines and sulphilimines, other sulphur-containing species gave rise to signals which were not easily distinguished from the 'rolling baseline'. Annunziata and Barbarella concluded that the

Table XIV: Sulphur-33 chemical shift data after Harris and Evans.[255]

Compound	δ(ppm)* in $CHCl_3$	Wl/2(Hz)
Me_2SO_2	320	50
Et_2SO_2	334	70
iPr_2SO_2	351	160
tBu_2SO_2	366	160
nPr_2SO_2	333	180
nBu_2SO_2	336	180
Ph_2SO_2	312	120
$(pCH_3C_6H_4)_2SO_2$	311	140
$(pHOC_6H_4)_2SO_2$	313	-
$(PhCH_2)_2SO_2$	330	120
Thiane-1,1-dioxide	322	50
Thiolane-1,1-dioxide	370	50
Butadiene sulphone	361	50

* Relative to external CS_2.

Table XV: Sulphur=33 nmr data after Annunziata and Barbarella.[256]

Compound	δ^* (ppm) in $CHCl_3$	Wl/2(Hz)
Me_2SO_2	315±1	40
Ph_2SO_2	308±1	100
4-Methylthiane-1,1-dioxide	321±1	70
3-Methylthiane-1,1-dioxide	322±1	90
$pMe\text{-}C_6H_4SO_2NH_2$	303±1	1400
Thiane	-30±8	8400
open chain: -S-		
-SO-		
-S-	too broad to to report data.	
$>C=S$		

* Relative to external CS_2

applications of sulphur-33 nuclear magnetic resonance are somewhat limited.

The sulphur-33 chemical shifts of some forty organic sulphur-containing compounds have been reported thus far in the literature. There have however, been two reference compounds used: 1) carbon disulphide.

2) a sulphate salt in water.

The aim of the current work was to increase the number of sulphur-33 chemical shifts for organic compounds and to try to correlate these results with structure and other spectral parameters.

CHAPTER 7

RESULTS AND DISCUSSION

The sulphur-33 chemical shifts and linewidths of twenty-seven sulphones were obtained using the experimental parameters described in Part IV (Experimental) of this thesis. Five of these compounds have been studied previously by three groups of workers, Faure et al.,[254] Harris and Evans[255] and Annunziata and Barbarella.[256] Figure XVIII shows four examples of the spectra obtained, these should be compared with the first 'resolved' proton nmr spectrum shown in Figure XVII. The origins of all of the compounds are detailed in the Experimental section. The data obtained in these experiments are given in Table XVI; δ-values are quoted relative to an external ~5M ammonium sulphate solution in water and have an uncertainty of less than one percent. A further eight compounds were also investigated but no resonance was observed for these. Some of these compounds were not soluble enough in $CDCl_3$ for a spectrum to be obtained.

Figure XVIII: Examples of sulphur-33 nmr spectra obtained in this study.

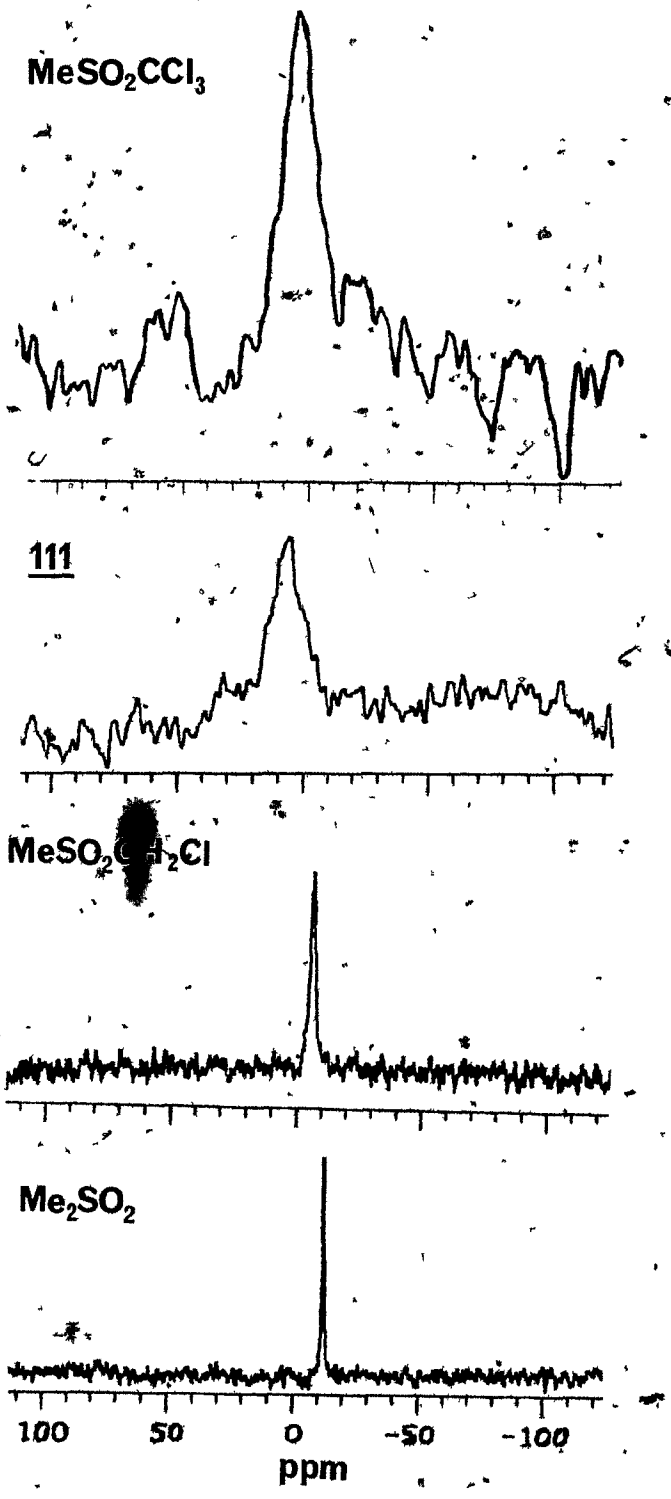


Table XVI: Sulphur-33 data for twenty-seven sulphones.

Entry	Formula	Compound number	δ_S	W1/2
1	$CH_3SO_2CH_3$	**177**	-12.8	15
2	$CH_3SO_2CH_2Cl$	**178**	- 7.16	90
3	$CH_3SO_2CHCl_2$	**179**	- 0.22	280
4	$CH_3SO_2CCl_3$	**180**	4.53	300
5	$CH_3SO_2CH_2Br$	**181**	-10.3	95
6	$CH_3SO_2CH(Cl)CH_3$	**182**	0.88	40
7	$CH_3SO_2CH_2Ph$	**183**	-16.7	40
8	$PhSO_2CH_2COCH_3$	**170**	-20.0	150
9	$PhSO_2CH_2COPh$	**166**	-18.8	350
10	$PhSO_2CH(SPh)COCH_3$	**172**	-17.0	350
11	$PhSO_2CH(Cl)CH_3$	**184**	- 6.56	50
12	$PhCH_2SO_2CH_2Ph$	**185**	- 3.30	15
13	$PhCH_2SO_2CH(Cl)Ph$	**186**	4.1	330

Table XVI: (cont.)

Entry	Formula	number	δ_S	W1/2
14	$PhCH_2SO_2CH(Cl)CH_3$	**187**	3.5	110
15	$PhCOCH_2SO_2CH_3$	**106**	-12.1	215
16	$PhCOCH(Cl)SO_2CH_3$	**112**	- 3.7	200
17	$PhCOCH(Br)SO_2CH_3$	**113**	- 5.0	400
18	$PhCOCH(SCH_3)SO_2CH_3$	**161**	4.0	325
19	$PhCOCH(SCH_2CH_3)SO_2CH_3$	**114**	5.9	120
20	$PhCOCH(SPh)SO_2CH_3$	**144**	4.0	400
21	$PhCOCH(CH_3)SO_2CH_3$	**165**	- 1.3	100
22	Thiane-1,1-dioxide	**158**	- 9.8	45
23	2-Chlorothiane-1,1-dioxide	**157**	- 9.6	100
24	$(CH_3)_2CHSO_2(CH_3)_2$	**188**	18.1	120
25	$CH_3CH_2SO_2CH_2CH_3$	**189**	4.92	50
26	$CH_3CH_2SO_2CH_2SO_2CH_2CH_3$	**190**	10.0	>500
27	$PhC(OCH_2CH_2O)CH_2SO_2CH_3$	**191**	-11.7	100

Choice of reference compound.

In this study, ammonium sulphate was chosen as the reference compound, i.e. it is defined as having a sulphur-33 chemical shift of zero. In the previous chapter, the use of two different reference materials was discussed. Until 1973 the only reference compound used was carbon disulphide, which shows a relatively narrow linewidth and the spectrum can be easily obtained. In 1973 Lutz et al.[253] advocated the use of an aqueous solution of a sulphate salt as the standard for sulphur-33 chemical shift measurements. These authors found that the line position of such a standard varied very little with concentration, the spectrum was obtained more readily than for carbon disulphide and the resonance was much narrower, They concluded also that it would be more acceptable to use sulphate as the reference species since it appeared close to one end of the known sulphur-33 chemical shift range. (This is no longer true since Wasylishen et al.[249] have shown that the sulphur-33 chemical shift range extends nearly 400 ppm downfield of ammonium sulphate).

The only real disadvantages with this reference material are that most compounds measured to-date have a negative chemical shift and that the reference must be external for most compounds studied. This latter problem, however, normally applies to carbon disulphide

as well.

In the current study, ammonium sulphate has been chosen as the standard for sulphur-33 chemical shift measurements and it is somewhat fortuitous that the standard exhibits a resonance approximately in the centre of the chemical shift range observed here, with δ-values being observed in the range 0 ± 20 ppm.

Comparison of the results obtained in this study with those reported previously.

In order to convert δ-values relative to carbon disulphide to δ-values relative to ammonium sulphate an indirect approach had to be used. Harris and Evans[255] quote the chemical shift of dimethyl sulphone as 320 ± 1 ppm relative to carbon disulphide (see Table XIV, page 186) whilst in the present study it was found to be -12.8 ± 0.2 ppm (see Table XVI). Thus a correction factor of -332.8 ppm had to be applied in order to convert δ relative to carbon disulphide to δ relative to ammonium sulphate. This figure agrees well with the result of 332 ± 2 for the chemical shift of carbon disulphide obtained recently by Wasylishen *et al.*[249] Table XVII shows the sulphur-33 chemical shifts of the five compounds common to this work and that of Harris and Evans.[255] Faure *et al.*[254] have quoted the chemical shift of dimethyl sulphone as -7 ± 1.5 ppm. relative to

Table XVII:

Compound	δ-values of S-atom ref to $(NH_4)_2SO_4$. Harris and Evans.	This work
Me_2SO_2	-12.8	-12.8
Et_2SO_2	1.2	4.92
iPr_2SO_2	18.2	18.1
$(PhCH_2)_2SO_2$	- 2.8	- 3.30
Thiane-1,1-dioxide	-10.8	- 9.78

ammonium sulphate; however, they used d_6-DMSO as solvent which is expected to exhibit different solvent effects compared with $CDCl_3$ (the solvent of choice in the present study). Also, the data of Faure, et al. were obtained in a low-field nmr spectrometer which means that the uncertainty in their chemical shift values is relatively large. Their results will thus not be discussed further here. Since the only compound common to the current study and that of Annunziata and Barbarella[256] is dimethyl sulphone, no useful comparisons can be made with their results.

Table XVII shows that only the result for diethyl-sulphone differs significantly between the present work and that of Harris and Evans.[32] The similarities shown in this table give us confidence that our results are meaningful. All the resonances observed in the present study, as reported in Table XVI, are narrower than those of Harris and Evans (see Table XIV, Chapter 6).

The present study confirms the previous observations that sulphur-33 nmr can be used to study mixtures in a qualitative manner. Two spectra were recorded, one of a mixture of $CH_3SO_2CH_2Cl$ and $CH_3SO_2CHCl_2$ and the other of $PhCOCH_2SO_2CH_3$ and $PhSO_2CH_2COCH_3$. In both cases resonances were observed with chemical shifts (within experimental error) identical to those quoted in Table XVI. Thus, the present results indicate that sulphur-33

nmr can be used to estimate the number of different sulphones in a molecule, or in a mixture. As more chemical shifts of different sulphones are reported, structural correlations will undoubtedly become possible, as indicated in the following section.

Correlation of chemical shifts obtained in this study with carbon-13 data.

The presentation of scientific data is an important part of the interpretation of that data. It has long been the goal of scientists to obtain linear relationships between new data and established parameters. Some workers have gone to great lengths, such as six-parameter fits, in order to obtain linear plots for their data; the interpretation of such correlations must be quite speculative.

In this context, it is intriguing to note that several groups of workers have found that the oxygen-17 chemical shifts of open-chain and polycyclic ethers[257] as well as of oxiranes,[258] amongst others, correlate linearly with the carbon-13 chemical shifts of the corresponding alkanes (i.e. the oxygen atom replaced by a methylene group). These studies have involved a range of alkyl groups, both acyclic and cyclic; however, no heteroatomic substituents, such as halogens, were studied.

Table XVIII shows the sulphur-33 chemical shifts obtained in the present study together with the carbon-13 chemical shift (obtained from the literature or by calculation, see Appendix IV) of the substituted alkane shown, i.e. a comparison of the structures **192** and **193** Table XVIII shows the data separated into five groups,

$R-SO_2-R'$ **192**

$R-CH_2-R'$ **193**

namely, those corresponding to the general structures **194**, **195** and **196**, those containing α-SR groups and others. The first three groups show linear correlations (see Figures XIX, XX and XXI). The last two structural types do not show useful correlations.

$R-SO_2-R$

R = alkyl

194

$PhSO_2CHXY$

195

RCH_2SO_2CXYZ

R = H or Ph

196

Table XVIII: Sulphur-33 and carbon-13 chemical shift data for twenty-seven related compounds.

Entry	Sulphone	δ_S	Substituted Alkane	δ_C*	ref
1	$MeSO_2Me$	+12.8	$MeCH_2Me$	16.1	259
2	$EtSO_2Et$	4.92	$EtCH_2Et$	34.6	259
3	$iPrSO_2iPr$	18.1	$iPrCH_2iPr$	49.1	260
4	$PhSO_2CH(Cl)Me$	6.56	$PhCH_2CH(Cl)Me$	47.9	
5	$PhSO_2CH_2COMe$	-20.0	$PhCH_2CH_2COMe$	29.8	260
6	$PhSO_2CH_2COPh$	-18.8	$PhCH_2CH_2COPh$	30.0	260
7	$PhCH_2SO_2CH_2Ph$	- 3.30	$PhCH_2CH_2CH_2Ph$	32.9	260
8	$PhCH_2SO_2Me$	-16.7	$PhCH_2CH_2Me$	24.8	261
9	$MeSO_2CH_2Cl$	- 7.16	$MeCH_2CH_2Cl$	26.3	261
10	$MeSO_2CHCl_2$	- 0.22	$MeCH_2CHCl_2$	37.3	
11	$MeSO_2CCl_3$	4.53	$MeCH_2CCl_3$	48.3	
12	$MeSO_2CH(Cl)Me$	0.88	$MeCH_2CH(Cl)Me$	33.8	262
13	$MeSO_2CH_2Br$	-10.3	$MeCH_2CH_2Br$	26.3	261
14	$PhCH_2SO_2CH(Cl)Ph$	4.10	$PhCH_2CH_2CH(Cl)Ph$	44.3	
15	$PhCH_2SO_2CH(Cl)Me$	3.50	$PhCH_2CH_2CH(Cl)Me$	44.1	
16	$PhCOCH(SEt)SO_2Me$	5.90	$PhCOCH(SEt)CH_2Me$	23.3	

Table XVIII: (cont.)

Entry	Sulphone	δ_S	Substituted Alkane	δ_C*	ref
17	$PhCOCH(SPh)SO_2Me$	4.00	$PhCOCH(SPh)\underline{C}H_2Me$	23.3	
18	$PhSO_2CH(SPh)COMe$	-17.0	$Ph\underline{C}H_2CH(SPh)COMe$	37.8	
19	$PhCOCH(SMe)SO_2Me$	4.00	$PhCOCH(SMe)\underline{C}H_2Me$	23.3	
20	$(EtSO_2)_2CH_2$	10.00	$Et\underline{C}H_2CH_2SO_2Et$	26.1	259
21	$PhCOCH(Br)SO_2Me$	- 5.00	$PhCOCH(Br)\underline{C}H_2Me$	27.3	
22	Thiane-1,1-dioxide	- 9.78	Cyclohexane	27.1	259
23	$PhCOCH(Me)SO_2Me$	- 1.30	$PhCOCH(Me)\underline{C}H_2Me$	26.1	
24	$PhCOCH_2SO_2Me$	-12.1	$PhCOCH_2\underline{C}H_2Me$	17.7	263
25	2-Chlorothiane -1,1-dioxide	- 9.60	Chlorocyclo-hexane (C-2)	36.9	260
26	$PhC(OCH_2)_2CH_2Ms$	-11.7	$PhC(OCH_2)_2\underline{C}H_2Et$	40.3	
27	$PhCOCH(Cl)SO_2Me$	- 3.70	$PhCOCH(Cl)\underline{C}H_2Me$	27.3	

* Calculated δ-value using the method of Lindeman and Adams[264,265] unless a reference number appears in the next column. For details of calculations see Appendix IV.

Figure XIX: A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure **194**.

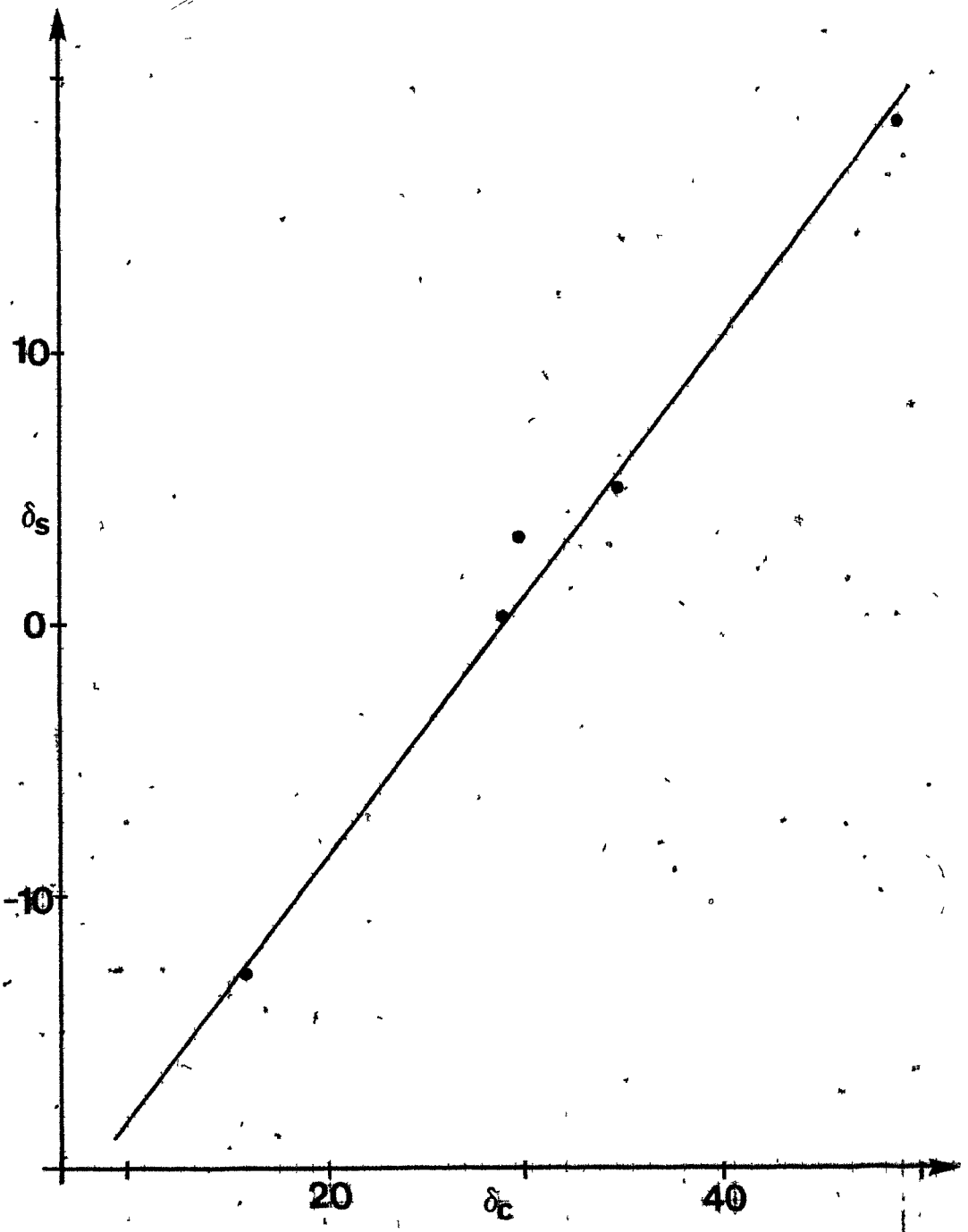


Figure XX: A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure 195 .

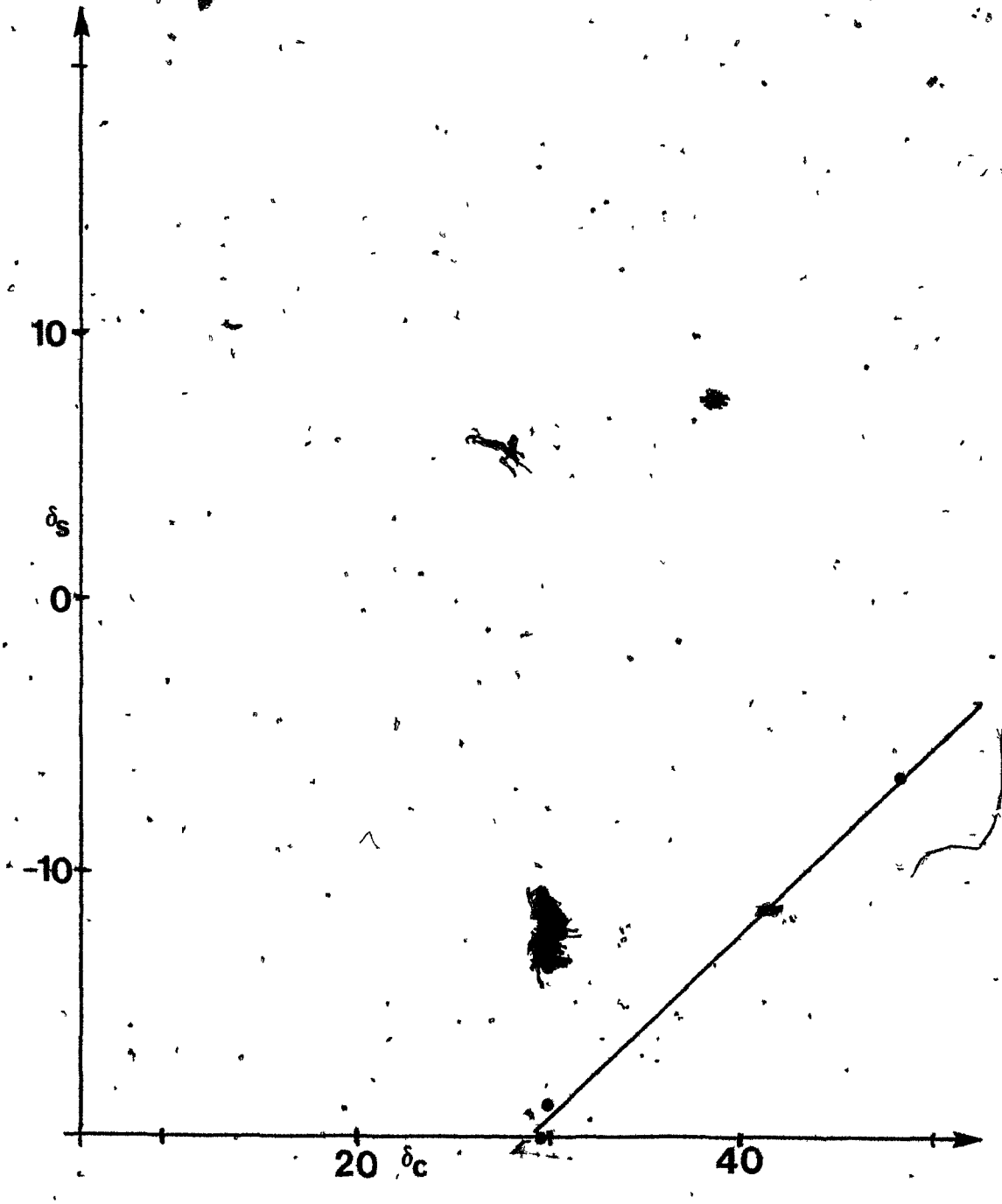
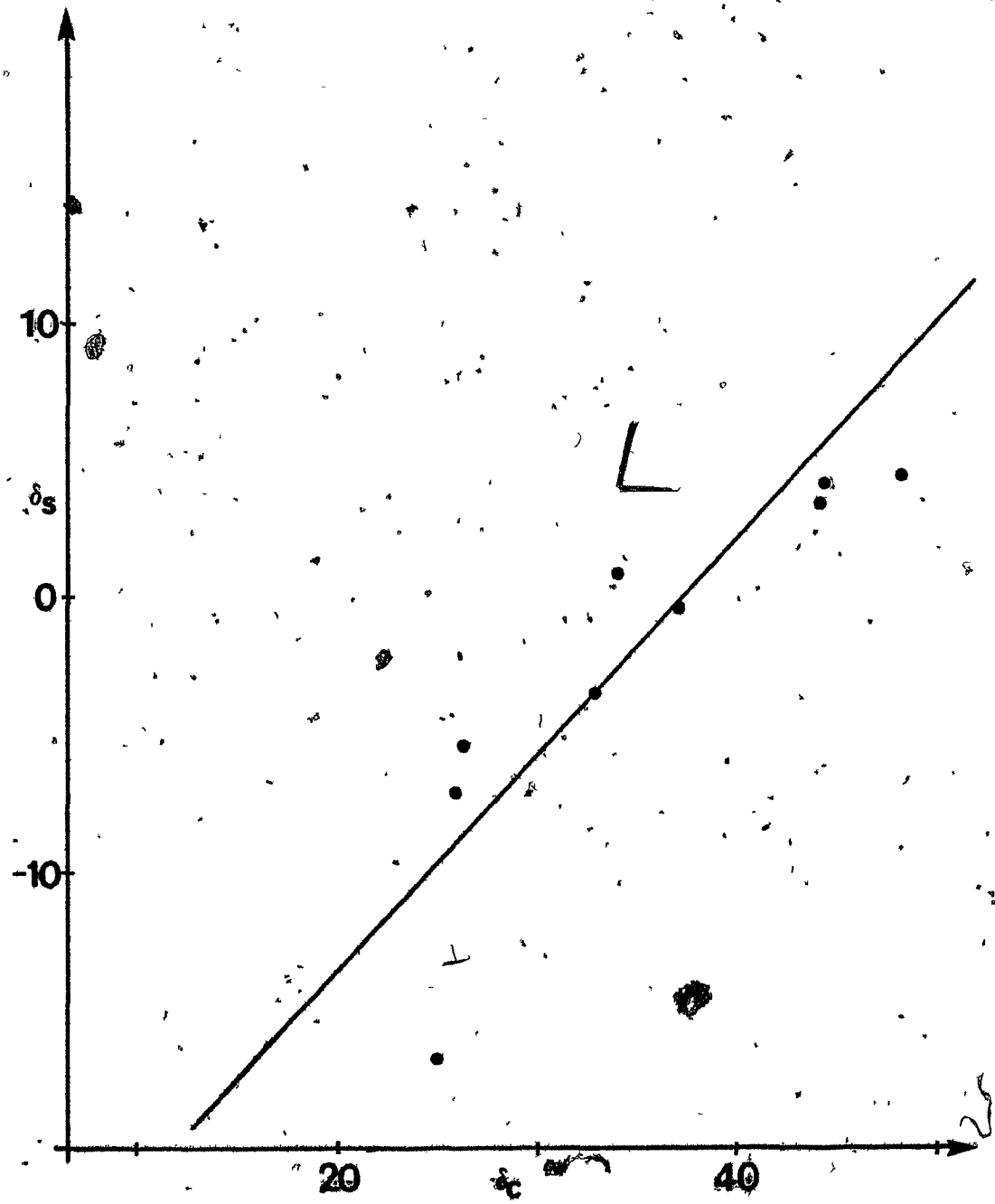


Figure XXI: A plot of sulphur-33 versus carbon-13 chemical shift values for compounds with structure **196** .



Presentation of the correlations.

The best linear correlation is obtained for the symmetrical dialkyl sulphones (entries 1-3 in Table XVIII). These three compounds give an excellent straight line with a slope of 0.94 and an intercept of -27.78 as indicated by the correlation coefficient of 0.9999. Inclusion of the data for di-n-propylsulphone (δ_S=0.2) and di-n-butylsulphone (δ_S=3.2) both obtained by Harris and Evans[255] together with the corresponding carbon-13 chemical shift values (29.0 and 29.6 respectively)[264] gives a line with a slope of 0.92 and an intercept of -26.48 together with a correlation coefficient of 0.992. This correlation is the one plotted in Figure XIX. As was mentioned earlier, the sulphur-33 resonance for diethyl sulphone obtained in the present study differed significantly from that reported by Harris and Evans.[245] Our sulphur-33 datum for this compound gives a much better linear correlation than does that of this other study as is evident from the respective correlation coefficients (0.992 vs 0.977).

Inclusion of the datum for di-t-butylsulphone from the work of Harris and Evans[255] (δ_S= 33.2) together with the corresponding carbon-13 chemical shift (δ_C = 56.5)[264] deleteriously effects the correlation. These six data points yield a line with a slope of 1.07 and an intercept of -30.42 whilst the correlation coefficient

drops to 0.987. It is unclear whether this sixth sulphur-33 chemical shift is erroneous or whether it is the effect of a sterically crowded t-butyl group which affects the correlation. It is felt however that the data of Harris and Evans should be treated with some care due to the known difference for diethyl sulphone.

The plot for the second structural type, **195**, gives a good correlation; the data are plotted in Figure XX and give a straight line with a slope of 0.71 and an intercept of -40.75. The correlation coefficient of 0.997 is excellent considering the differences in the structures of these compounds. The plot for the third structural type, **196** is seemingly more scattered (see Figure XXI) however, the nine points used in the regression analysis yield a line with a slope of 0.76 and an intercept of -29.69. The correlation coefficient of 0.909 must be considered in the light of the very varied structures of these nine compounds. For both of these plots the slope of the regression line is 0.7-0.8 indicating that the sulphur atom is significantly less sensitive to its overall environment than is the carbon atom in the corresponding substituted alkane, when probed by nuclear magnetic resonance measurements.

Of the remaining compounds, entry #18 in Table XVIII, $PhSO_2CH(SPh)COCH_3$, fits the line for compounds of

structural type **195**. If these data are included in the

$PhSO_2CHXY$

195

regression analysis the correlation coefficient drops to 0.89. Since the other α-SR substituted sulphones do not fit any of the correlations it seems reasonable not to include entry #18 in the correlation shown in Figure XX. None of the other compounds in the table (entries 16, 17, 19, 21) fit any reasonable correlations. It should be noted that many of the carbon-13 chemical shifts in these groups were calculated; these chemical shifts may therefore lack accuracy (see discussion in Appendix IV).

Correlation of sulphur-33 chemical shifts with oxygen-17 data.

The oxygen-17 chemical shift results for simple ethers correlate well with carbon-13 data for the corresponding alkanes.[257] In the present study, the sulphur-33 chemical shifts for simple dialkyl sulphones correlated well with the relevant carbon data (vide infra). Thus, it seemed reasonable to

investigate a correlation of sulphur-33 nmr data with the corresponding oxygen-17 data. Such a correlation would be expected to be good, and if so this will indicate consistency amongst the three sets of data.

Table XIX lists the oxygen-17 and sulphur-33 chemical shifts for seven simple ethers and the corresponding sulphones. Regression analysis produces a straight line with a slope of 0.30 and an intercept of 2.38 with a correlation coefficient of 0.998 for the first four on the list. Thus a very good correlation is produced indicating consistency of all the data and this is plotted in Figure XXII. Inclusion of the last three sets of data progressively worsens the correlation (r=0.991, 0.985 and 0.920).

Discussions of the correlations.

In the recent literature there have been several reports concerning the linear correlation of oxygen-17 nmr data with carbon-13 data from the relevant hydrocarbon. The most notable of these are the papers published by Kintzinger and his co-workers[257,266], concerning the oxygen-17 data obtained from cyclic and acyclic ethers. Calculations by these workers based on theoretical considerations have shown that the slope of the correlation for a homologous series of compounds

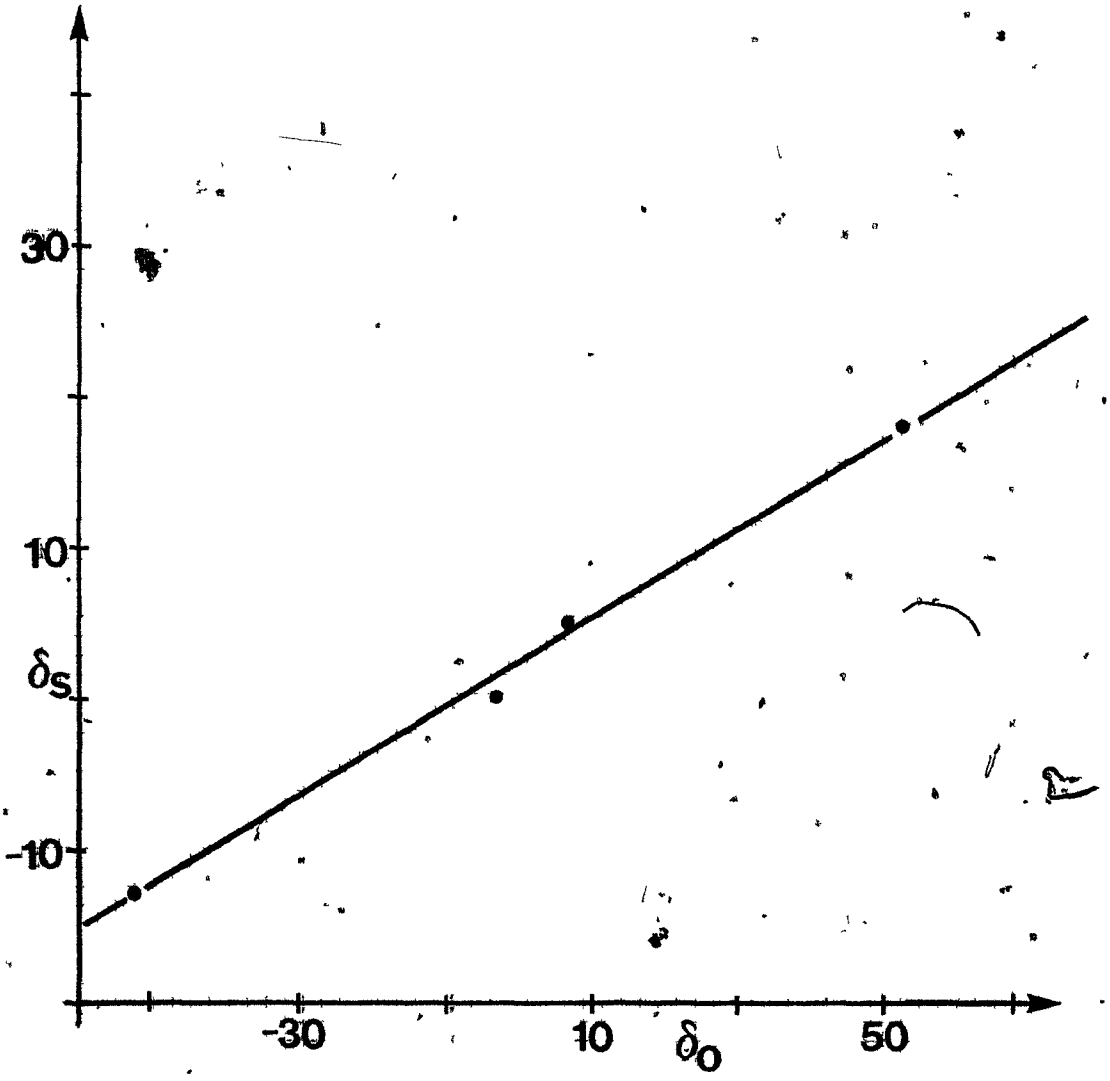
Table XIX: Oxygen-17 and sulphur-33 chemical shifts for simple ethers and sulphones.

Sulphone	δ_S	Ether	δ_{O^+}
$MeSO_2Me$	-12.8	MeOMe	-52.5
$EtSO_2Et$	4.92	EtOEt	6.5
$iPrSO_2iPr$	18.1	iPrOiPr	52.5
$nPrSO_2nPr$	0.2*	nPrOnPr	- 3.5
$nBuSO_2nBu$	3.2*	nBuOnBu	- 7.0
$tBuSO_2tBu$	33.2*	tBuOtBu	76.0
Thiane-1,1-dioxide	- 9.78	Tetrahydrofuran	5.0

* Data after Harris and Evans.[255]

+ Data after Nguyen et al.[257]

Figure XXII: A plot of sulphur-33 versus oxygen-17 chemical shift values for simple ethers and sulphones.



should be 2.3. For the dialkyl ethers the experimental data give a slope of 3.2. Although Kintzinger has indicated that these two figures agree rather well[257] it is felt that better calculations would be valuable.

The data presented in the current study do not fit the calculation mentioned above. This is not suprising however, since the calculation depends on the nature of the atomic orbitals of oxygen; this will be different for sulphur where 3p rather than 2p, and possibly 3d, orbitals are involved. It should also be noted that the comparison of oxygen-17 nmr results for ethers and sulphur-33 nmr results in sulphones is unlikely to be valid due to many reasons, for example, whereas sulphones are particularly affected by adjacent polar groups, this is not so for ethers. A sulphide is much more akin to an ether and such a comparison may be more instructive. Unfortunately there have been few reliable reports of sulphur-33 nmr measurements of sulphides (see Chapter 6). This is due to the fact that the sulphenyl sulphur nucleus has a very unsymmetrical field gradient and the natural linewidths are large due to quadrupolar relaxation.

It has been suggested by Iwamura et al.[258] that the slope of the linear correlation of oxygen-17 versus carbon-13 chemical shifts gives a measure of the relative sensitivity of the oxygen-17 and carbon-13

nuclei to their local environment in an nmr measurement. Using this idea the data presented in this study show that in the case of dialkyl sulphones the sulphur-33 nucleus is as sensitive to its environment as is the carbon nucleus in the corresponding hydrocarbon (i.e. slope is approximately unity). For the other structural types, **195** and **196**, the sulphur nucleus is less sensitive to its environment compared with the carbon (i.e. slope is <0.8 cf 0.94). This observation does not seem to fit the well established properties of sulphones. It is well known (see also Part II of the present work) that the presence of the sulphone moiety in an organic molecule often has a significant effect on the conformational preference of the molecule *via* a through-space electronic interaction; this has been discussed in Chapter 5. A better explanation of the data obtained in the present study is presented below.

It is proposed that the apparent low sensitivity of the sulphur-33 nucleus in a sulphone may be explained by a consideration of nuclear screening. This is the property which causes nuclei of the same type in different environments to possess different chemical shifts.

The overall screening constant, σ, of a nucleus can be divided into the sum of two parts; the screening caused by local electrons, σ_A (i.e the bonding and non-bonding electrons around the nucleus) and the screening

caused by the rest of the environment, σ_B. This latter

$$\sigma = \sigma_A + \sigma_B$$

constant would be expected to be dependent on the solvent used and is observed with changes in chemical shift with solvent. For second-row elements such as carbon and oxygen it is usual to ignore the effects of the rest of the molecule, for a particular solvent system, and just to consider the local electrons for nuclear screening. Since the sulphur atom is larger than oxygen and since it is well known that sulphones in particular have a marked effect on local substituents, it is felt likely that these substituents will also have some measurable effect on the sulphone, and hence the nucleus, and thus the chemical shift of this nucleus. If the screening caused by this type of effect was of opposite sign to that of the screening constant caused by the local nuclear environment then this would tend to lessen the total screening (which is related to the quantity measured by the slope in the correlations). So in contrast to what seems to be lower sensitivity it may be suggested that the sulphur nucleus is also sensitive to its nuclear environment, in fact more so than carbon-13 or oxygen-17, but that this increased sensitivity is

masked by two opposite effects. In the case of the compounds with highly electronegative substituents, such as in **195**, one would expect a larger contribution to the screening from the rest of the molecule and hence the apparent sensitivity in this type of compound would be lowered still further. Such a lowering is indeed observed.

Until more data are available little can be said about the information gathered for the compounds in Table XVIII (entries 17-28) which are not part of the correlations present.

Summary.

In this preliminary study the chemical shifts and linewidths of twenty-seven sulphones have been presented. It has been shown that the data obtained in this study are consistent with that published to-date. There is a good correlation of sulphur-33 versus carbon-13 chemical shift data for symmetrical dialkyl sulphones and correlations with two other structural types do exist, but these are not as well defined. An explanation for the apparent low sensitivity of sulphur-33 relative to carbon-13 has been given.

Although it was made in 1979 the following quotation still has merit:

> 'In spite of numerous investigations, the effect of substituents on n.m.r. chemical shifts cannot yet be interpreted in a completely satisfactory way.'
>
> Ewing and Toyne.[267]

Suggestions for further work.

Since all the dialkyl sulphones studied here were symmetrical it would probably be useful to synthesize some symmetrically substituted haloalkyl sulphones such as $(ClCH_2)_2SO_2$. These compounds should show reduced linewidths compared with similar unsymmetrical compounds since a more symmetrical field gradient around sulphur atom will lead to reduced relaxation by quadrupolar mechanisms. Obviously, it will also be desirable to prepare more compounds with a planned series of structures so as to improve the correlation coefficients in the plots of sulphur-33 *versus* carbon-13 chemical shift. More accurate calculation of the chemical shifts of the corresponding hydrocarbons or measurement of the actual chemical shifts after synthesis of the compounds would also help improve the correlations.

Further work in the area of sulphur-33 nuclear magnetic resonance will surely lead to the increased use of this technique for the study of organo-sulphur containing species.

PART IV

EXPERIMENTAL, APPENDICES AND REFERENCES

CHAPTER 8

EXPERIMENTAL

General

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

Infra-red spectra were recorded on one of three grating spectrophotometers: a Pye-Unicam SP1000, a Perkin-Elmer model 237B or 283B. Samples were analysed either in the form of a KBr disc or as a solution in chloroform, as specified. All spectra were calibrated with polystyrene film using the 2851 cm^{-1} and 1603 cm^{-1} absorption bands and are reported in wave numbers (cm^{-1}).

Routine nuclear magnetic resonance spectra were recorded on a Varian T-60 or a Varian CFT-20 spectrometer. Chemical shifts are reported as delta (δ) values relative to an internal standard of tetramethylsilane (for proton) or the line at 1538.0 Hz due to the central peak of $CDCl_3$ (for carbon-13).

High-field carbon-13 and proton nmr spectra were obtained, where appropriate, on a Nicolet Model 360NB spectrometer, coupled to an Oxford Instruments Superconducting magnet and a Nicolet 192 kword data acquisition system. These spectra were recorded by the staff of the Atlantic Regional Magnetic Resonance

Centre, Halifax, N.S. and the author is indebted to these workers.

Ultra-violet - visible absorption spectra were recorded on a Cary-Varian 219 spectrometer and are reported in nanometers.

Mass spectra were obtained with a Dupont-CEC model 21-104 mass spectrometer. Samples were introduced directly into the source using a glass probe and with the ionization voltage set at 70 eV unless otherwise stated. Spectra are reported as m/z values (Daltons) followed by the relative intensity of the peaks in parenthesis.

Elemental analyses were performed by either Guelph Chemical Laboratories Ltd., Guelph, Ontario or Canadian Microanalytical Service, Ltd., Vancouver, British Columbia and agreed within ±0.4% of the calculated values.

X-ray data for the determination of structures were collected on an Enrauf-Nonius CAD-4 four-circle diffractometer with automatic data collection utilising a PDP8/a computer system (Digital Equipment Corp.). Subsequent operations were carried out on a CYBER 170-720 (Control Data) computer. These X-ray data were measured and calculated by Professor T.S. Cameron and his co-workers and the author is greatly indebted to these scientists.

Materials

Starting materials were obtained from BDH, Fisher or Aldrich as appropriate. If possible ACS grade compounds were used, if not then reagent grade chemicals were usually used after purification. All solvents were routinely distilled prior to use. Dry acetonitrile was prepared by rapid distillation from phosphorus pentoxide, dry benzene was prepared by initially shaking with calcium chloride followed by storage over sodium wire. Other dry solvents were stored over 4A molecular sieves, except THF which was freshly distilled from $LiAlH_4$ immediately before use. 'Petrol' refers to petroleum ether which boils in the range 40-60°C.

Pure phenylmethanesulphonyl chloride was donated by Prof. J. A. Pincock to whom the author is grateful. All other sulphonyl chlorides were distilled from phosphorus pentoxide no more than one week prior to use. Triethylamine was distilled from potassium hydroxide pellets and stored in a desiccator. All dimethylamino-containing aromatic compounds were purified by first passing a methylene chloride solution of the amine down an alumina column followed by evaporation of the solvent and distillation *in vacuo*.

Sulphur-33 Nuclear Magnetic Resonance Spectra

The sulphur-33 nuclear magnetic resonance spectra reported in this thesis were obtained using the Nicolet 360NB nuclear magnetic resonance spectrometer, as described above. The author is indebted to the staff of the Atlantic Regional Magnetic Resonance Centre, Halifax, N.S., Canada for the acquisition of these spectra.

The spectrometer frequency used was 27.716172 MHz with quadrature detection and a total sweep width of 5000 Hz. A pulse width of 35 μs (90^{o}-pulse) with a pulse delay of 1s between pulses. A delay of approximately 200 μs was used between pulse and acquisition in order to eliminate the effects of acoustic ringing and hence rolling base line and the spectrum was collected over 819.2 ms (aquisition time) and stored using 16k data points. The probe temperature was 20 ± 1^{o}C and typically 500-10000 transients were collected; a Butterworth filter was used for all measurements.

The spectrometer was locked on deuterium which was used for shimming purposes. An external standard of 5M ammonium sulphate in water was used in order to report chemical shift values. Samples were run in regular 10mm nmr tubes in $CDCl_3$ solution and were typically 100-500mg of sample per 2ml of solvent. Chemical shift values are reported with an uncertainty of ±1%.

pKa measurements

The combined glass electrode used for pH measurement was one manufactured by Orion Research (model 91-02) which was connected to an Orion Research model 601 digital pH meter. Measurements were carried out in a Blue M Electrical Company Magni Whirl constant temperature bath (model no: MW -1120A-1) set at 30 ± 1°C. Titrations were performed in a Teflon beaker and the standard base solution (~0.8M) was added using a Gilmont ultra-precision burette which had a maximum capacity of 2.5ml with scale divisions every 0.0001ml.

Acid solutions were made up in 50% ethanol - 50% water (prepared by mixing 50g of super-dry ethanol with 50g of quartz-distilled water which had been boiled to remove carbon dioxide). The base was made up in carbon dioxide-free water and was standardised by titration against potassium hydrogen phthalate.

The pH meter was checked before and after each pK_a determination with aqueous 0.05M potassium hydrogen phthalate (pH = 4.10 at 30°C [156]) and 0.052M sodium tetraborate (pH = 9.20 at 30°C [156]). The pK_a determination was rejected if the pH readings of these buffers were not within 0.05 pH units. During the titration, readings were taken as soon as the pH became stable. A typical set of results are shown in Table XX for compound **167**. Three pK_a determinations per compound

Table XX: Results of a pK_a determination of 167.

pH	Volume of base added	ΔpH	1/ΔpH
6.82	0		
		1.08	0.93
7.90	0.0200		
		0.37	2.70
8.27	0.0400		
		0.25	4.00
8.52	0.0600		
		0.20	5.00
8.72	0.0800		
		0.20	5.00
8.92	0.1000		
		0.17	5.88
9.09	0.1200		
		0.17	5.88
9.28	0.1400		
		0.21	4.76
9.49	0.1600		
		0.28	3.57
9.77	0.1800		
		0.43	2.33
10.20	0.2000		
		1.10	0.91
11.30	0.2200		
		0.90	1.11
12.20	0.2400		
		0.32	3.13
12.52	0.2600		
		0.18	5.56
12.70	0.2800		
		0.14	7.14
12.84	0.3000		

were carried out wherever possible. Figure XXIII presents these data in a graphical form and Figure XXIV is the corresponding Gran plot. The uncertainty in most of the pK_a values is ±0.1 pK_a units. The pK_a of **167** determined graphically is 9.21 whilst that determined using the equation given in Chapter 5 is 9.05.

Vacuum-assisted chromatography

Relatively rapid, cheap column chromatography was carried out using a column of tlc grade silica gel as the stationary phase and petroleum ether - methylene chloride mixtures as eluant. The flow rate was increased by attaching a water vacuum pump to the bottom of the column. Fractions (usually 50ml) were collected by the use of a 'six-flask pig' similar to that used as a vacuum-distillation receiver, These were monitored by the use of tlc or proton nmr as appropriate.

Preparation of compounds.

Preparation of bis(methylsulphonyl)-3-(2,6-dimethoxypyridyl)sulphonylmethane, 48.

A mixture of 2,6-dimethoxypyridine (2.9ml, 0.022mol), methanesulphonyl chloride (9.57ml, 0.125 mol) and acetonitrile (30ml) was cooled to -20° to -30°C

Figure XXIII: A plot of pH versus volume of base added for 167

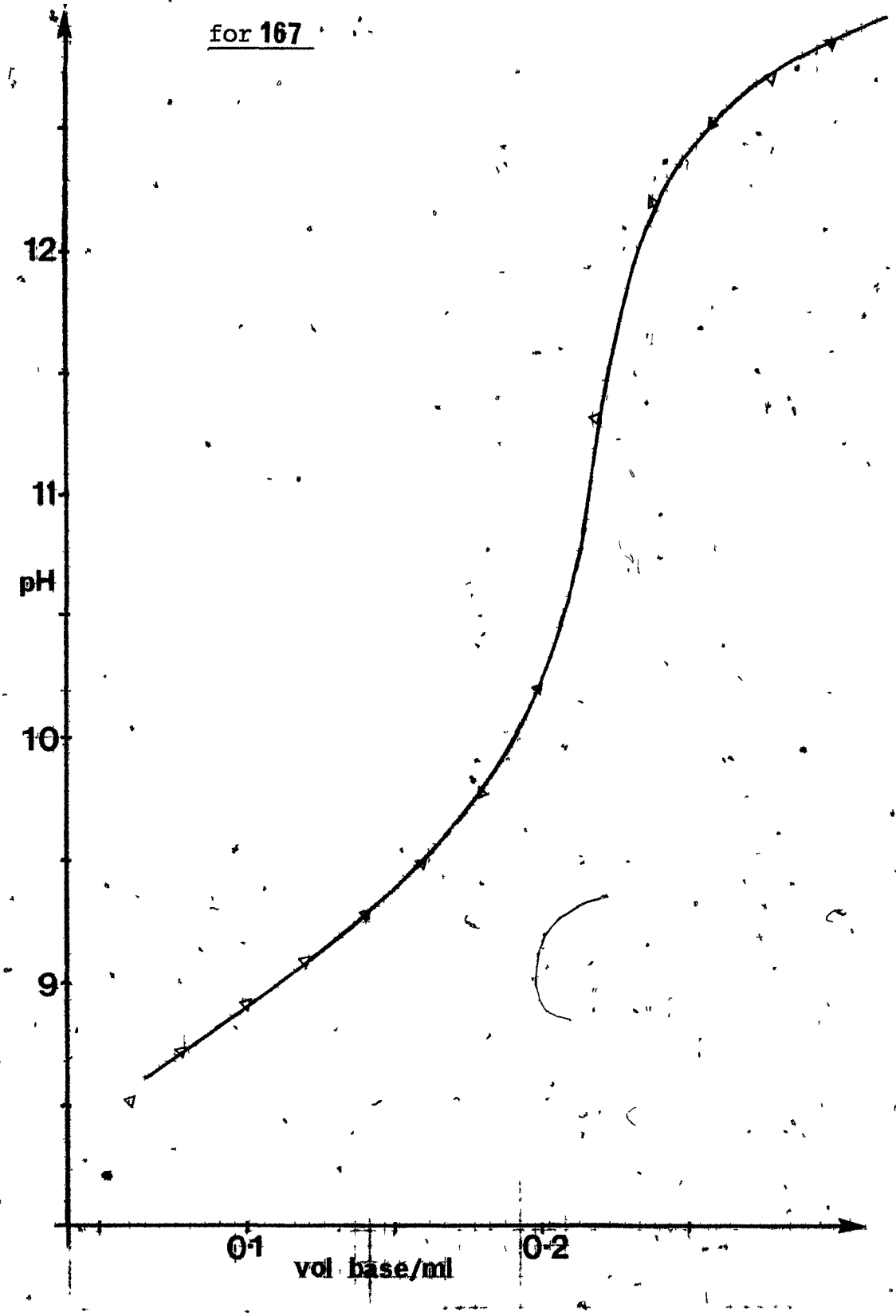
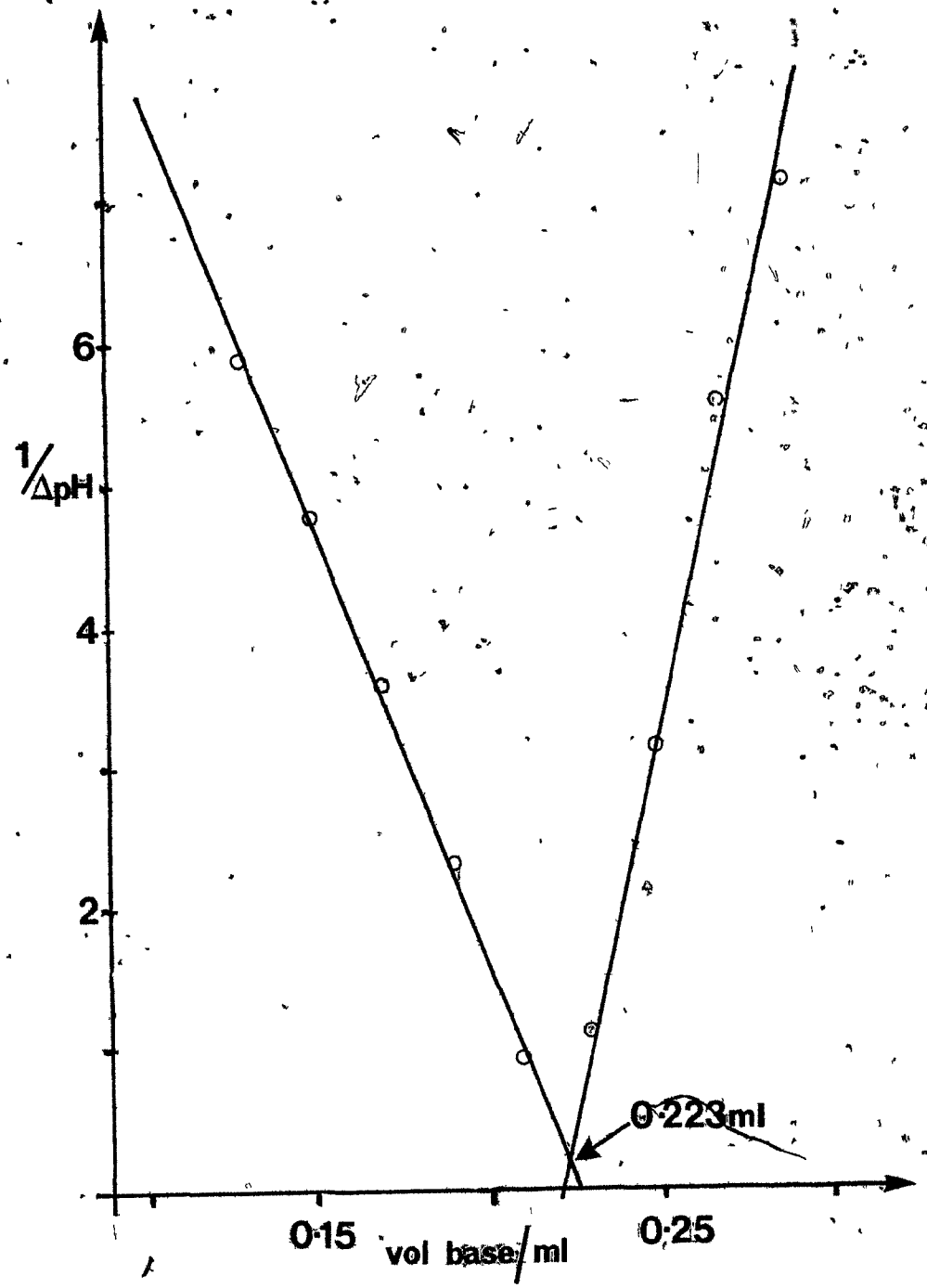


Figure XXIV: A plot of $1/\Delta$ pH versus volume of base added for 167 (Gran plot).



(acetone/liq. N_2 bath) and stirred, under dry nitrogen for 15 minutes. Triethylamine (17.5ml, 0.125mol) in acetonitrile (35ml) was added dropwise over a half-hour period and the mixture was then stirred for a further ninety minutes at reduced temperature. After allowing the mixture to warm up to room temperature the acetonitrile was removed and the resulting brownish-yellow oil was scratched and cooled in methanol. The solid produced (1.86g) was recrystallised from boiling methanol yielding colourless prisms of 48 (0.82g, 10%) mp: 217-9°C.

ir (KBr disc):	2900, 1585, 1480, 1465, 1385, 1340, 1285, 1235, 1190, 1155, 1120, 1060, 990, 965, 810.
ms:	373(6,M^+), 294(6), 202(100), 156(39), 138(8), 131(94), 108(69), 93(33), 80(13), 79(28), 69(78).
^{1}H nmr (d_6-DMSO):	3.46 (d,6H,J=0.6Hz;$\underline{Me}SO_2$)
	3.99 (s,3H; OMe)
	4.13 (s,3H; OMe)
	6.50 7.96 (AB pattern)
^{1}H nmr($CDCl_3$):	as above plus:
	5.71 (m,1H, exch., J=0.6Hz; $SO_2\underline{CH}Ms_2$

^{13}C nmr (d_6-DMSO):	44.85 (q,2C; $SO_2\underline{Me}$)
	54.53 (q; O<u>Me</u>)
	54.71 (q; O<u>Me</u>)
	90.15 (d; <u>C</u>H(Ms_2)
	102.16 (d; py-C-5)
	143.98 (d; py-C-4)
	159.87 (s; py-C-3)
	165.94 (s; py-2 or 6)
	166.71 (s; py-2 or 6)
uv (+HCl):	λ_{max} 285, 234, 214
uv (neutral + NaOH):	λ_{max} 285, 244, 208

A CHS elemental analysis agreed with an empirical formula of $C_{10}H_{15}NO_8S_3$ (expected 32.17% C, 4.02% H and 25.74% S; observed 32.31% C, 4.06% H and 25.45% S).

<u>Preparation of the potassium salt, **51**</u>

A mixture of **<u>48</u>** (0.1001g. 2.7×10^{-4}mol) and KOH (0.1g, 1.8×10^{-3}mol) in water (10ml) was warmed and stirred for 10 minutes and then left to cool. The solution was acidified with glacial acetic acid (0.5ml), and on standing needle shaped crystals of **<u>51</u>** (0.102g, 92%), the required salt, were formed. The crystals gave a positive K-flame test (lilac) and decomposed on heating to 248°C.

ir (KBr disc):	3475, 3060, 2950, 1570,
	1460, 1360, 1310, 1260(s),

1230, 1120, 1080, 1045, 985, 800.

Crystal data:

$K^+(C_{10}H_{14}NO_8S_3)^-.H_2O$,

monoclinic, a = 17.826(3), b = 6.919(3), c = 15.085(2) Å, α = 111.90(1)°, space group $P2_1/c$, Z=4, D_c = 1.65g cm^{-3}, Mo-$K_{\alpha 1}$ radiation, λ = 0.70926 Å, μ = 6.43 cm^{-1}. 2750 unique reflections were collected of which 1150 had $I > 3\sigma(I)$ and were used. R=0.033.

Preparation of bismethylsulphonyl-4-(1,3-dimethoxyphenyl)sulphonylmethane, **55**

The procedure used was as for the preparation of **48** except that 1,3-dimethoxybenzene (2.85ml, 0.022mol) was used as the aromatic compound. The solid produced on scratching was recrystallised from methanol yielding colourless needles of **55** (3.0g, 36.7%). It should be noted that 1.74g of the starting material was recovered after scratching thus the effective yield of **55** is increased to 87%, mp = 215-6°C.

ir(KBr disc): 3005, 2915, 1595, 1480, 1465, 1330, 1210, 1150, 1065, 1015, 965, 845, 780

ms: 372(0.7,M^+), 293(1), 201(100).

^{1}H nmr ($CDCl_3$)	3.47 (d,6H,J=0.6Hz,$MeSO_2$)
	3.89 (s,3H,MeO)
	3.99 (s,3H,MeO)
	5.83 (m,each,1H,J=o.6Hz)
	6.55, 7.83, 7.94 (ABX pattern, 3H).
^{13}C nmr (d_6-DMSO):	44.79 (q, 2xc, SO_2Me)
	56.13 (q, OMe)
	56.89 (q, OMe)
	90.59 (d,$\underline{C}H(SO_2Me)_2$)
	98.99 (d)
	105.78 (d)
	118.89 (s)
	132.89 (d)
	158.94 (s)
	166.37 (s)

Crystal data:

$C_{11}H_{16}O_8S_3$, triclinic, a = 8.888(3), b = 13.096(5), c = 14.983(3) Å, α = 68.012(28)°, β = 81.450(22)°, γ = 72.606(30)°, space group $P\bar{1}$, Z = 4, D_c = 1.60gcm^{-3}. Mo - Kα_1 radiation, λ = 0.70926 Å, μ = 4.52 cm^{-1}. 3244 unique reflections were collected of which 2573 had $I > 3\sigma(I)$ and were used.

R = 0.064.

Preparation of 2,4-dimethoxy-1-methylsulphonylbenzene,56

Procedure as for **55** except the reaction was stopped after forty-five minutes. Work-up followed by extraction of the resultant oil with 5% NaOH solution left a methylene chloride soluble oil which on scratching yielded **56** (0.14g, 3%) mp: 101-3°C, lit. 103-5°C.[74]

^{13}C nmr ($CDCl_3$): 42.85 (q, $\underline{Me}SO_2$)
55.53 (q, $\underline{Me}O$)
55.99 (q, $\underline{Me}O$)
99.13 (d)
104.44 (d)
120.44 (s)
131.10 (d)
158.46 (s)
165.31 (s)

Reaction of N,N-dimethylaniline with sulphene

The reaction was carried out as for preparation of except that the aromatic substrate was N,N-dimethylaniline (2.67g, 0.022 mol).* The resulting residue after evaporation of the acetonitrile was washed with petroleum ether which produced N,N-dimethylaniline (1.21g) after evaporation. The residue remaining was

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* different ratios of sulphene: N,N-dimethylaniline were used as detailed in Table II (page 50).

greenish-blue and was separated by vacuum-assisted chromatography as described above.

For the reaction with a sulphene - N,N-dimethylaniline ratio of 2.5:1 the following compounds were obtained in the quantities given:

Methylsulphonyl-4-(N,N-dimethylanilino)sulphonylmethane, **58** - (2.38g, 72%), mp: 181-3°C colourless needles from methanol or methylene chloride.

4-Methylsulphonyl-N,N-dimethylaniline, **65** - (0.02g, 1%), colourless needles mp: 162-4°C, lit. 165-6°C.[88,96]

N-Methyl-N-methylsulphonylaniline, **66** - (0.19g, 8%), colourless needles mp:73-4°C.

2,4'-Dimethylamino-5-methylsulphonylbiphenyl, **68** -(0.10g, 5%), mp: 147-8°C, yellow needles from methanol.

The yields for other ratios of N,N-dimethylaniline to sulphene are given in Table II (page 50).

For **58** :

ir (KBr disc): 3010, 2910, 1595, 1525, 1445, 1380, 1320, 1295, 1210, 1140, 1095, 1085, 990, 965, 845, 815, 775, 730, 710, 565, 515, 500.

ms: 277(72,M^+), 184(51), 168(14), 136(100), 134(75), 120(62), 119(20), 118(24), 105(20), 104(13), 91(13), 79(17), 77(18), 63(15).

^{1}H nmr (d_6-DMK): 3.05 (s,6H, $\underline{Me}_2N$), 3.31 (s,3H, $\underline{Me}SO_2$), 4.92 (s, 2H, $SO_2\underline{C}H_2SO_2$), 6.81, 7.85 (AA'BB' pattern).

^{13}C nmr (d_6-DMSO): 40.60 (q,2C, $N\underline{Me}_2$), 43.29 (q, $\underline{Me}SO_2$), 72.95 (t, $SO_2\underline{C}H_2SO_2$), 111.65 (d, 2C), 124.05 (s), 131.27 (d, 2C), 154.67 (s).

uv (MeOH): λ_{max} 296, 216.

A CHNS elemental analysis agreed with an empirical formula of $C_{10}H_{15}NO_4S_2$ (expected 43.32%C, 5.42%H, 5.05%N and 23.10%S; observed 43.37%C, 5.46%H, 5.09%N and 23.14%S).

For **66**:

ms: 186(10,M+1), 185(100,M^+), 107(11), 106(97), 105(10), 104(11), 79(10), 78(6), 77(30), 64(4), 51(6).

^{1}H nmr ($CDCl_3$): 2.83(s,3H,MeN),
3.32(s,3H,$MeSO_2$),
7.30-7.43(m,5H)

^{13}C nmr ($CDCl_3$): 35.04 (q),
37.90 (q),
126.00 (d,2C),
127.23 (d),
129.13 (d,2C),
141.27 (s).

For 68:

ir (KBr disc): 3000, 1615, 1510, 1490,
1450, 1390, 1350, 1300,
1230, 1140, 1060, 945,
810, 530.

ms: 318(31,M^+), 241(19),
240(100), 239(8), 238(6),
225(12), 224(13), 223(7),
209(4), 152(6), 140(7),
120(8), 119(14), 111(5).

Also a plethora of metastable ion peaks and peaks due to doubly and triply charged ions were present.

^{1}H nmr ($CDCl_3$): 2.80(s,6H,NMe_2),
3.00(s,6H,NMe_2),
3.34(s,3H,$MeSO_2$),

6.8, 7.5 (AA'BB' pattern),
7.44, 7.76 8.23 (ABX pattern).

^{13}C nmr ($CDCl_3$): 40.42 (q),
42.66 (q),
46.27 (q).
112.67 (d, 2C),
123.84 (d),
126.74 (d),
127.10 (s),
127.58 (d, 2C),
131.70 (d),
136.98 (s),
138.51 (s),
150.29 (s),
151.50 (s).

uv (MeOH): $\lambda_{max.}$ 306.

uv (MeOH + HCl): $\lambda_{max.}$ 300, 246.

A CHNS elemental analysis agrees with an empirical formula of $C_{17}H_{22}N_2O_2S$ (expected 64.15%C, 6.92%H, 8.81%N and 10.06%S; observed 63.91%C, 6.87%H, 8.51%N and 10.21%S).

Preparation of methylsulphonyl-4-(N,N-dimethyl-1-napthylamino)sulphonylmethane, 59

The preparation was as described for 48 except that N,N-dimethyl-1-napthylamine (3.77g, 0.022mol) was used in place of 2,6-dimethoxypyridine. Work-up produced 59 (2.7g, 84% based on recovered starting material). Recrystallisation from methanol or from ethyl acetate-petroleum ether yielded slightly yellow, needle-shaped crystals with mp: 193-4 °C.

ir (KBr disc): 2970, 2910, 1565, 1505, 1420, 1385, 1305, 1215, 1195, 1145, 1110, 1045, 955, 885, 840, 805, 765, 540, 495.

ms: 327(0.8,M^+), 186(3), 172(10), 171(100), 170(58), 169(7), 168(7), 155(8), 154(12), 128(17), 127(11), 121(11).

^{1}H nmr ($CDCl_3$): 3.04(s,6H,$\underline{Me}_2N$), 3.29(s,3H,$\underline{Me}SO_2$), 4.68(s,2H,$SO_2\underline{CH}_2SO_2$), 6.96 -8.50 (m,6H),

^{13}C nmr ($CDCl_3$): 42.83 (q,2C,$N\underline{Me}_2$), 44.46 (q,$\underline{Me}SO_2$),

72.30 (t,$SO_2\underline{C}H_2SO_2$),
110.71 (d),
123.13 (d),
125.48 (d,2C),
126.42 (d,2C),
128.94 (s),
133.68 (s,2C),
158.20 (s).

Preparation of methylsulphonyl-4-(N,N,3-trimethyl-anilino)sulphonylmethane, **60**

The procedure was as for the preparation of **48**. Use of N,N-dimethyl-m-toluidine (2.97g, 0.022mol) yielded **60** (2.3g, 84% based on recovered starting material) on work-up. The product was purified by passage down a short silica column and was recrystallised from ethyl acetate-methylene chloride or from acetone yielding colourless needles mp: 121° (decomp.).

ir (KBr disc): 3010, 2970, 2910, 1595, 1545, 1450, 1365, 1320, 1295, 1215, 1175, 1155, 1120, 1040, 965, 845, 790, 760, 500.

ms: 293(10,M+2), 292(15,M+1), 291(100,M^+), 198(22),

182(5), 151(16), 150(71), 149(13), 148(33), 135(18), 134(71), 120(11), 119(7), 118(14), 91(20), 89(5), 79(7), 77(9), 65(7), 63(7).

^{1}H nmr ($CDCl_3$): 3.04 (s,6H,$\underline{Me}_2N$), 3.22 (s,3H,$\underline{Me}SO_2$), 4.50 (s,2H,$SO_2\underline{CH}_2SO_2$), 6.47-7.85 (ABX pattern,3H).

^{13}C nmr ($CDCl_3$): 21.02 (q,$\underline{Me}$Ar), 39.77 (q,2C, $N\underline{Me}_2$), 42.47 (q,$\underline{Me}SO_2$), 72.76 (t,$SO_2\underline{CH}_2SO_2$), 108.51 (d), 114.06 (d), 120.77 (s), 133.14 (d), 139.68 (s), 153.93 (s).

uv (MeOH): λ_{max} 297, 220.

Preparation of methylsulphonyl-2-(N-methyl-pyrrolo)sulphonylmethane, **72**

The procedure was as for the preparation of **48**. Use of N-methylpyrrole (1.78g, 0.022mol) prepared by a

similar method to that reported previously[268] (bp 112-3°C) yielded **72** (2.1g, 81% based on recovered starting material) as colourless needles after recrystallisation from ethyl acetate-petroleum ether, mp: 136-7°C.

ir (KBr disc): 3110, 3030, 3010, 2980, 2950, 2915, 1585, 1510, 1395, 1320, 1220, 1165, 1120, 1050, 1010, 975, 915, 860, 805, 765, 745, 705, 690, 625, 595,

ms: 239(7,M+2), 238(7,M+1), 237(74,M^+), 222(5), 146(6), 145(8), 144(100), 130(8), 128(9), 110(5), 97(6), 96(83), 94(41), 81(77), 80(70), 79(10), 67(5), 53(17), 52(10).

^{1}H nmr ($CDCl_3$): 3.26 (s,3H,$\underline{Me}SO_2$), 3.96 (s,3H,$\underline{Me}N$), 4.60 (s,2H, $SO_2\underline{CH_2}SO_2$), 6.18-7.17 (m,3H).

^{13}C nmr ($CDCl_3$): 35.51 (q,N$\underline{Me}$), 41.98 (q,$\underline{Me}SO_2$), 73.28 (t,$SO_2\underline{CH_2}SO_2$), 108.31 (d),

120.75 (d),
131.45 (d),
136.90 (s).

Reaction of N,N-dimethylaniline with methanesulphonyl chloride in the presence of antimony pentachloride.

A mixture of N,N-dimethylaniline (6.0g, 0.05mol), methanesulphonyl chloride (5.7g, 0.05mol) and antimony pentachloride (12.8ml, 0.1mol) wae refluxed in carbon disulphide solution (180ml) for four hours under a dry nitrogen atmosphere. After this time the reddish-brown heterogeneous mixture was poured into ice-water (120ml); the layers were separated and the aqueous layer was extracted with methylene chloride (3 x 80ml). The combined organic layers were washed with water (3 x 80ml) and dried with magnesium sulphate. Evaporation yielded a two-phase residue which was extracted with petroleum ether. Evaporation of the petrol produced N,N-dimethylaniline (3.6g). The petrol-insoluble residue was dissolved in methylene chloride (100ml) and this solution was washed with sodium hydroxide solution (2 x 50ml, 2.5%) and then with water (2 x 50ml); after drying and evaporation a green solid was obtained. Column filtration using silica gel yielded a colourless solid which was recrystallised from ethanol producing **68** (1.3g, 41% based on recovered starting material). All the

spectral properties of this product were as for **68** produced in the reaction of N,N-dimethylaniline with sulphene.

Reaction of N,N-dimethylaniline with antimony pentachloride.

This reaction was carried out exactly as for the preparation of **68**, above, except that no methanesulphonyl chloride was added to the mixture. Work-up allowed N,N-dimethylaniline (4.2g) to be recovered. Column filtration produced no useful separation and so vacuum assisted column chromatography was used (the method is described above). Many fractions were collected and these yielded impure samples; a mass spectrometric analysis of these indicated the presence of **78-82**. One almost pure fraction yielded, 2,4'-dimethylaminobiphenyl, **77** as a yellow oily solid.

For **77**:

ms: 242(2,M+2), 241(19,M+1), 240(100,$M^{+\cdot}$), 239(9), 226(7), 225(22), 224(10), 152(9), 120(14), 119.5(8), 119(19).

^{1}H nmr ($CDCl_3$): 2.76 (s,6H,NMe_2), 2.93 (s,6H,NMe_2),

6.75, 7.16 (AA'BB'pattern), 6.98, 7.16, 7.76, 7.94 (ABCD pattern).

For **78**-**82**:

ms: 310(6), 309(3), 308(12, M^+ for **82**), 307(3), 306(6, M^+ for **81**), 288(8), 279(7), 277(6), 276(31), 275(20), 274(100, M^+ for **80**), 273(18), 272(55, M^+ for **79**), 259(17), 258(6), 256(6), 255(17), 254(79, M^+ for **78**), 253(32), 241(17), 240(82, M^+ for **77**), 239(9), 225(14), 224(10), 152(17).

Reaction of 1,3-dimethoxybenzene with antimony pentachloride

The procedure for this reaction was that used for the reaction of N,N-dimethylaniline with antimony pentachloride alone. The aromatic substrate used here was 1,3-dimethoxybenzene (6.9g, 0.05mol). Work-up yielded an oil which on trituration with petrol allowed the recovery of 1,3-dimethoxybenzene (2.9g). The residue that was left was sublimed and then recrystallised from

aqueous ethanol yielding 1,5-dichloro-2,4-dimethoxybenzene, **83**, as colourless needles (3.3g, 55%), mp: 115-7°C. lit. 117-8°C.[106]

ir (KBr disc):	2980, 2940, 2900, 1580, 1495, 1460, 1430, 1375, 1300, 1230, 1210, 1170, 1085, 1020, 860, 800, 740.
ms:	208(64), 207(10), 206(100 $M^{+\cdot}$), 193(8), 191(12), 165(26), 163(40), 150(5), 148(7), 122(2), 120(5), 113(5), 99(5), 97(6).
^1H nmr ($CDCl_3$):	3.91 (s,6H,MeO), 6.53 (s,1H), 7.35 (s,1H).

Reactions using phenylsulphene and methylsulphene.

These reactions were carried out under the same conditions as used for the reaction of sulphene itself the only difference being that phenylmethanesulphonyl chloride was used.

Work-up of the reaction mixture followed by column chromatography using petroleum ether and silica gel yielded the starting aromatic substrate in nearly

quantitative yield and trans-stilbene, mp: 120-2°C).[269]

Preparation of ethyl (N-chlorosulphonyl)carbamate.

A three-necked, 100ml, round-bottomed flask was fitted with a thermometer, condenser and a pressure-equalising dropping funnel under a dry nitrogen atmosphere. Chlorosulphonyl isocyanate (3.5ml, 0.040mol) and dry methylene chloride (10ml) were placed in the flask and then stirred mechanically. Ethanol (2.35ml, 0.040mol) in methylene chloride (5ml) was then added dropwise over a two hour period. During this time the temperature was kept below 25°C with a cold water bath.

Upon evaporation of the solvent on a rotary evaporator a colourless oil remained which solidified on cooling. This solid was rapidly recrystallised from benzene-methylene chloride yielding white crystals (7.05g, 94%) of ethyl (chlorosulphonyl)carbamate. On exposure to light, ethyl (N-chlorosulphonyl)-carbamate decomposes, indicated by a distinct darkening of the solid. Consequently, once isolated, all operations with this compound were done rapidly and when possible were shielded from light. The solid was stored in a brown bottle, in a desiccator and used within seven days of preparation.

Preparation of other (chlorosulphonyl)carbamate esters.

These compounds were prepared by a similar method to that used above except that the corresponding alcohol or phenol (0.041mol) was used. Recrystallisation from carbon tetrachloride-methylene chloride yielded white crystals of the (chlorosulphonyl)carbamate esters (80-95%). These compounds were also unstable.

Preparation of ethylsulphamoyl chloride.

This compound was prepared according to the reported procedure of Kloek and Leschinsky.[34] Ethylsulphamoyl chloride was obtained in 71% after distillation, bp 60-1°C/ 2mmHg (lit. 52°C/ 0.05mmHg[32]).

Preparation of N,N-dimethyl-N'-ethylsulphanilamide, 89

A solution of ethylsulphamoyl chloride (3g, 0.02mol) and N,N-dimethylaniline (2.42g, 0.02mol) in dry tetrahydrofuran (50ml) was stirred at 10-20°C under a nitrogen atmosphere, To this was added a solution of triethylamine (3ml, excess) in THF (20ml) dropwise over half an hour. The reaction mixture was then stirred at room temperature for two hours after which it was poured into water (100ml) and acidified. This mixture was extracted with methylene chloride (5 x 35ml) and the organic layers were combined, dried and then evaporated to dryness. The residue remaining was

triturated with petrol and the solid left was recrystallised from methylene chloride-petrol yielding colourless needles (2.5g, 55%), mp: 158-9°C (lit. 160-62°C[47]).

ir (KBr disc): 3345, 2970, 1605, 1510, 1370, 1315, 1150, 870.

^{1}H nmr (d_6-DMK): 1.06 (t,3H), 2.54 (q, 2H), 3.06 (s,6H), 6.65, 7.65 (AA'BB' pattern),

Preparation of 2,4-dimethoxy-N-ethylsulphonamide, **90**

The reaction was carried out as for the preparation of **89** except 1,3-dimethoxybenzene was used in place of N,N-dimethylaniline. Recrystallisation from ethanol yielded colourless needles of **90** (54%), mp: 120-1°C.

ir (KBr disc): 3320, 3060, 2980, 2940, 1580, 1470, 1460, 1440, 1410, 1320, 1290, 1260, 1220, 1155, 1130, 1070, 1020, 945, 835, 805, 765, 675, 580.

^{1}H nmr (d_6-DMK): 1.03 (t,3H), 2.18 (q,2H), 3.92 (s,3H),

3.99 (s,3H),
5.89 (br, exch.,1H),
6.54, 7.83, 7.93,
(ABX pattern,3H).

^{13}C nmr (d_6-DMK): 14.52 (q),
38.21 (t),
55.49 (q),
55.86 (q),
99.26 (d),
104.82 (d),
120.91 (s),
131.65 (d),
158.32 (s),
164.90 (s).

Preparation of N,N-dimethyl-N'-carboethoxy-sulphanilamide, **91**

A mixture of carboethoxysulphanoyl chloride (2g, 0.01mol) and N,N-dimethyaniline (1.21g, 0.01mol) was dissolved in sodium dried benzene. Triethylamine (25ml, excess) in dry benzene (25ml) was added dropwise over a half-hour period and the mixture was then stirred for a further two hours at room temperature. After this time the reaction was poured into ice-water (100ml), acidified with hydrochloric acid and extracted with methylene chloride (4 x 30ml). After drying the organic

layer with magnesium sulphate it was evaporated in vacuo yielding **91** as colourless crystals after recrystallisation from methylene chloride-petrol (1.65, 61%), mp: 187-8°C (lit. 184-90°C[47]).

ir (KBr disc): 3395, 3005, 1735, 1600, 1475, 1340, 1150, 1130.

^{1}H nmr ($CDCl_3$): 1.23 (t,3H), 3.07 (s,6H), 4.13 (q,2H), 6.68, 7.83, (AA'BB' pattern).

^{13}C nmr ($CDCl_3$): 13.97 (q), 39.89 (q,2C), 62.58(t), 110.38 (d,2C), 122.99 (s), 130.16 (d,2C), 150.62 (s), 153.46 (s,C=O).

Preparation of N,N-dimethylsulphanilamide, **92**

A solution of **91** (1.5g, 0.006mol) and hydrochloric acid (80ml, 10% excess) was refluxed for one hour. After this time the solution was neutralised with sodium hydroxide and on evaporation to a small volume a solid

precipitated. Recrystallisation from aqueous ethanol yielded colourless needles of **92** (1.1g, 92%), mp: 213-14°C, lit. 200-6°C.[270]

ms: 202 (7,M+2), 201 (22,M+1), 200 (100,M^+), 199 (37), 184 (9), 136 (40), 120 (22), 119 (7), 105 (7), 104 (6), 77 (8), 42 (6).

^{13}C nmr (d_6-DMK): 41.1 (q,2C,NMe_2), 112.4 (d,2C), 128.8 (d,2C), 131.7 (s), 153.9 (s).

Preparation of 2,4-dimethoxy-N-carboethoxy-benzenesulphonamide, **93**.

The procedure was as for preparation of **91** except that 1,3-dimethoxybenzene (1.38g, 0.01mol) was used. Recrystallisation from ethanol yielded colourless needles of **93** (34%), mp: 142-4°C.

^1H nmr ($CDCl_3$): 1.22 (t,3H), 4.10 (q,2H), 3.91 (s,3H), 3.98 (s,3H), 6.42, 7.75, 7.89,

(ABX pattern).

^{13}C nmr ($CDCl_3$): 13.97 (q), 55.41 (q), 55.81 (q), 62.05 (t), 99.70 (d), 104.82 (d), 121.43 (s), 131.65 (d), 153.33 (s), 157.35 (s), 162.99 (s),

Preparation of 2,4-dimethoxybenzenesulphonamide, **94**.

The procedure followed was as for preparation of **93**. Recrystallisation from ethanol yielded **94** (96%) as colourless lathes, mp: 165-6°C.

ir (KBr disc): 3395, 3290, 2995, 1605, 1570, 1490, 1460, 1410, 1320, 1250, 1210, 1165, 1145, 1075, 1020, 925, 890, 870, 830.

ms: 219 (6,M+2), 218 (11,M+1), 217 (100,M^+), 201(49), 170(6),

153(21), 135(8),
123(6), 122(46),
107(28), 92(9),
79(10), 77(15),
64(6), 63(9).

^{1}H nmr (d_6-DMK): 3.88 (s,3H),
3.97 (s,3H),
6.13 (br, exch, 1H),
6.68, 6.68, 7.72,

^{13}C nmr (d_6-DMK): 56.10 (q,OMe),
56.80 (q,OMe),
99.7 (d),
104.4 (d),
117.9 (s),
129.5 (d),
156.9 (s),
161.7 (s).

Reactions of sulphur trioxide complexes with aromatic compounds.

A mixture of either anisole or 1,3-dimethoxybenzene or N,N-dimethylaniline (1mol eq) with either SO_3-pyridine or SO_3-NMe_3 (2mol eq) was heated for six hours in a sealed tube at a fixed temperature. After this time the tube was cooled and opened and carefully neutralised with cold dilute hydrochloric acid (2M). The solvent was

then evaporated *in vacuo* using a boiling water bath. The residue was triturated with petroleum ether to remove the unreacted aromatic species. Any remaining residue was then carefully recrystallised from ethanol-water yielding colourless needles of 2,4-dimethoxybenzenesulphonic acid, **97** and N,N-dimethylamino-*p*-benzenesulphonic acid, **98** in some cases. The yields resulting from these reactions and the temperatures employed are detailed in Table III in Chapter 3.

For **97**:

mp:	263°C (decomp.) leaflets.
ir (KBr disc):	3500, 2970, 2940, 1650, 1600, 1580, 1490, 1450, 1410, 1290, 1255, 1210, 1180, 1150, 1030, 1020, 910, 825, 800.
^{1}H nmr (D_2O):	3.05 (s,3H), 3.89 (s,3H), 6.63, 6.67, 7.70. (ABX pattern).

For **98**:

mp:	269-70°C (decomp.) irregular plates.
^{1}H nmr (D_2O):	3.32 (s,6H), 7.71, 8.00, (AA'BB' pattern).

^{13}C nmr (D_2O): 46.26 (q,2C);
121.28 (d,2C);
128.06 (d,2C);
154.78 (s).

Preparation of 2-methylsulphonyl-1-phenylethanone, **106**.

Sodium hydride (9.44g, 50% suspension in oil, 0.197 mol) was washed with dry petroleum ether (3 x 40ml) to remove the oil. To this gray powder was added dimethyl sulphone (18.49g, 0.197 mol) in dimethyl-sulphoxide (100ml) under an atmosphere of dry nitrogen. The mixture was stirred and heated to 50-55°C (the temperature being measured in the reaction mixture) for one hour and then cooled in an ice bath. Ethyl benzoate (15ml, 0.10 moles) was then added and the solution was stirred at room temperature for 30 minutes and then for a further 90 minutes at 55-60°C. After cooling the reaction mixture was poured into ice-water (100ml) and acidified to pH = 7 with concentrated HCl. The combined organic layers were extracted into methylene chloride (4 x 50ml) followed by copious washing with water (7 x 40ml) and drying with magnesium sulphate. Evaporation *in vacuo* yielded 16.4g (84%) of the crude product which smelled like rotting cabbage. Recrystallisation from toluene (x2) produced colourless needles of **106**, 2-methylsulphonyl-1-phenylethanone in 81% yield (15.7g)

which was tlc pure (chloroform as eluent, SiO_2).
mp: 105-6°C, lit. 106-7[73], 2,4-Dinitrophenylhydrazone mp: 152-4°C.

ir ($CDCl_3$):	3030, 1670, 1590, 1320, 1155.
^1H nmr ($CDCl_3$):	3.16 (t,J=0.8Hz).
	4.60 (q,J=0.8Hz).
	7.4-8.1(m,5H).
^{13}C nmr ($CDCl_3$):	41.62 (q, J_{CH}=139.2Hz),
	60.97 (t, J_{CH}=137.1Hz),
	128.79 (d,2C),
	128.99 (d,2C),
	134.40 (d),
	135.50 (s),
	189.12 (s).

Preparations of 2-methylsulphonyl-1-phenylethanone, on a smaller scale, yielded typically 85-90%. This increased yield is probably due to better control of the reaction temperature.

Preparation of N-methylthiophthalimide, 111a

A mixture of dimethyl disulphide (8ml, 0.09 mol) in carbon tetrachloride (100ml) was stirred magnetically in a three-neck flask fitted with a condenser under an

atmosphere of dry nitrogen. This mixture was cooled in a dry ice-acetone bath* -20 to -30°C for 20 minutes. To this cold solution was added sulphuryl chloride (6.8ml, 0.085 mol) and the resultant yellow solution was stirred for two hours under these conditions. After this time a solution of phthalimide (23.5g, 0.16mol) in N,N-dimethylformamide (200ml) containing triethylamine (25ml, 0.18 mol, excess) was added and the cold-bath was retained for a further 30 minutes. The heterogeneous mixture was then allowed to warm to room temperature and was stirred for a further two hours. Rotary evaporation of the carbon tetrachloride followed by filtration yielded an almost quantitative yield of triethylamine hydrochloride (mp, proton nmr). Dilution of the remaining DMF solution with water (400ml) followed by cooling and filtration yielded an off-white solid which was taken up in cold methylene chloride: Phthalimide (10g) was left after attempted dissolution in methylene chloride. The methylene chloride solution was dried ($MgSO_4$), and evaporated under vacuum producing **IIIa** (11.7g, 66% based on recovered phthalimide) as a colourless crystalline solid mp: 159-61°C,

* The reaction was also attempted using an ice-bath in place of the dry-ice-acetone-bath, and the same procedure as outlined above. However, the yield was then reduced to 54%.

lit. 158-9°C.[271]

^{1}H nmr ($CDCl_3$): 2.55 (s,3H),
7.6-8.0 (m,4H).

^{13}C nmr ($CDCl_3$): 22.27 (q),
123.69 (d,2C),
131.98 (s),
134.44 (d,2C),
170.85 (s,C=O).

Preparation of N-ethylthiophthalimide, 111b

The procedure used was as for N-methylthiophthalimide except that diethyl disulphide (11ml, 0.09 mol) was used. The yield of product 111b, after recrystallisation was 68%, mp: 122-3°C, lit. 115°C.[271]

^{1}H nmr ($CDCl_3$): 1.30 (t,3H),
2.93 (q,2H),
7.6-8.0 (AA'BB'pattern).

^{13}C nmr ($CDCl_3$): 12.88 (q),
32.30 (t),
123.43 (d,2C),
131.65 (s),
134.24 (d,2C),
168.07 (s).

Preparation of N-phenylthiophthalimide, **111c**

A solution of diphenyldisulphide (8.72g 0.04 mol) in dry carbon tetrachloride (180ml) was magnetically stirred under dry nitrogen, and was cooled in an ice-bath for 15 minutes. Sulphuryl chloride (3.2ml, 0.04 mol) was added to this solution and the mixture was stirred for 2 hours at 0°C. After this time a solution of phthalimide (5.88g, 0.04 mol) and triethylamine (12ml, 0.086 mol) in N,N-dimethylformamide (80ml) was added. The resultant orange-brown mixture was stirred at 0°C for a half-hour and then at room temperature for a further two hours. Filtration of the mixture yielded triethylamine hydrochloride quantitatively as the residue. The filtrate was rotary evaporated rapidly to remove the carbon tetrachloride and was then diluted with water to 600ml total volume. The yellowish-white precipitate was filtered off, washed copiously with water and then dissolved in cold methylene chloride. A small amount of solid (0.2g) was insoluble in CH_2Cl_2 and was shown to be recovered phthalimide by proton nmr and melting point. After drying with magnesium sulphate the methylene chloride solution was rotary evaporated to yield a slightly yellow crystalline solid which on recrystallisation from methanol yielded 9.4g (92%) of **111c** with a melting point of 162-3°C, lit. 160-1°C.[271]

^1H nmr ($CDCl_3$): 7.0-8.0 (m).

^{13}C nmr ($CDCl_3$): 123.76 (d),
129.03 (d),
130.52 (d),
131.67 (d),
134.32 (s),
134.46 (d),
134.79 (s),
167.40 (s, C=O).

Preparation of 2-methylsulphonyl-1-phenyl-1-phenylthioethanone, **169**

A solution of 2-methylsulphonyl-1-phenylethanone (2.54g, 0.013 mol), N-phenylthiophthalimide (3.25g 0.013 and triethylamine (4.5ml, excess) in dry methylene chloride (100ml) was stirred under dry nitrogen at room temperature for 14 hours. Rotary evaporation followed by recrystallisation of the solid from methanol yielded phthalimide quantitatively (mp, ^1H nmr). The mother liquor was evaporated *in vacuo* and the residue was dissolved in methylene chloride (80ml). The organic layer was washed with HCl (3 x 25ml, 1M) and water (25ml) and then dried and evaporated giving a nearly white solid in 3.7g (93%) yield. Recrystallisation from ethanol-water gave **169** as colourless needle-shaped crystals with mp: 99-100.5°C

^{1}H nmr ($CDCl_3$):	3.30 (s,3H),
	5.61 (s,1H),
	7.2-8.1 (m,10H),
^{13}C nmr ($CDCl_3$):	37.68 (q,J=139.7Hz).
	72.69 (d,J=146.1Hz),
	128.89 (d,2C),
	129.42 (d,2C),
	129.59 (d,2C),
	131.34 (s),
	133.66 (d,2C),
	134.48 (s),
	189.90 (s,C=O).

Preparation of 1-methylsulphonyl butan-2-one, 128

Sodium hydride (0.48g of a 50% dispersion in oil, 0.01 mol) was placed in a 3-neck flask and washed with petrol (4 x 15ml) and then thoroughly dried under vacuum yielding a gray powder. The flask was flushed out with dry N_2 (several times) and then dimethyl sulphone (0.94g, 0.01 mol) in dry dimethyl sulphoxide (20ml) was added. The resulting mixture was stirred under dry nitrogen at 50-55°C for 2 hours. After this time, ethyl propionate (0.50g, 4.9 x 10^{-3} mol) in dry dimethyl sulphoxide (20ml) was added dropwise and then the resulting mixture was again stirred at 50-55°C for a further 2 hours. The reaction mixture was poured

into ice-water (100ml) and acidified (to pH <2) with concentrated HCl. This mixture was extracted with CH_2Cl_2, dried and evaporated *in vacuo* yielding, **128** as an off-white solid (0.70g, 95%) Purification by bulb-to-bulb distillation gave a solid with mp = 41-3°C (lit. 44.5-45.5°C[134]). The solid gave only one spot for the tlc in acetone (Rf = 0.86) and $CHCl_3$ (Rf = 0.51) visualised with iodine. The 2,4-dinitrophenylhydrazone was prepared, recrystallisation from aqueous ethanol giving a yellow solid with mp: 242-4°C.

ir (KBr disc):	2930, 1720, 1440, 1360, 1300, 1250, 1125, 1080, 1020, 940.
ms:	150 (4,M^+), 121(20), 94(5), 79 (46), 71 (5), 63 (7), 57 (100), 53 (6).
^1H nmr ($CDCl_3$):	1.10 (t,3H), 2.73 (q,2H), 3.05 (s,3H), 4.06 (s,2H),
^{13}C nmr ($CDCl_3$):	6.50 (q, ^1J=[illegible].1Hz; ^2J=3.9Hz; $\underline{C}H_3CH_2$-), 37.29 (t, ^1J=125.8Hz; q, ^2J=4.4Hz; $CH_3\underline{C}H_2$), 41.06 (q,J=138.9Hz;

$-SO_2\underline{C}H_3$),

63.42 (t,J=137.8Hz;

$-CO\underline{C}H_2SO_2-$),

199.87 (q, $-\underline{C}O-$).

Note: Larger scale preparations usually produced lower yields. This was probably due to difficulty controlling the reaction temperature.

Preparation of β-ketosulphones with a fatty chain, **130**

Fatty chain containing β-ketosulphones were also prepared using the molar quantities as for **128**. The products were all recrystallised from methanol.

Compound:	y(%):	mp(°C):
173 (n=10)	92	73-4
174 (n=12)	98	80-1
175 (n=14)	86	72-4
197 (n=16)	90	76-9

For **175**:

ir (KBr disc): 2920, 2850, 1720, 1470, 1400, 1375, 1360, 1305, 1135, 1070, 970, 710, 515.

ms: 332 (1,M^+), 253 (7), 252 (31), 239 (5), 235 (5), 234 (13), 196 (8), 194 (14), 149 (28),

139 (10), 138 (20),
137 (87), 136 (93),
121 (47), 111 (27),
109 (27), 98 (20),
97 (80), 95 (53), 93 (13),
83 (77), 81 (77), 79 (100),
71 (70), 69 (62), 64 (12),
57 (6), 55 (5).

^{1}H nmr ($CDCl_3$): 0.88 (t,3H),
1.25 (br s, 26H),
2.70 (t,2H),
3.04 (s,3H),
4.01 (s,2H).

^{13}C nmr ($CDCl_3$): 13.94, 22.55, 22.90,
28.71, 29.22 (2C),
29.52 (7C), 31.79, 37.62,
41.37 (q, $SO_2\underline{Me}$),
44.78 ($\underline{C}H_2CO$),
64.52 (t, $CO\underline{C}H_2SO_2$),
199.59 ($\underline{C}$=O).

for 197: ms: 358 (1,M^+), 340 (4), 327 (4),
281 (18), 280 (40), 267 (9),
263 (6), 262 (14), 149 (12),
138 (10), 137 (40),
136 (38), 125 (14),
121 (11), 111 (16),

109 (16), 97 (11), 96 (41), 95 (14), 94 (28), 83 (20), 82 (11), 81 (37), 80 (13), 79 (28), 77 (18), 71 (13), 69 (44), 68 (12), 67 (38), 65 (18), 53 (65), 39 (100).

Spectra for **173** and **174** were appropriately similar to those examples given above.

Reaction of **128** with morpholine to produce **160**

A mixture of **128** (1.0g, 6.67×10^{-3} mol), morpholine (0.73 ml, xs), p-toluenesulphonic acid (0.1g) and benzene (40ml) were refluxed for 48 hours using a Dean-Stark trap. The solvent was then evaporated and the residue was redissolved in CH_2Cl_2 (50ml), this was then extracted with 5% KOH (to remove unreacted **128**). The organic layer was then dried and evaporated and the residue was recrystallised from petroleum ether-ethyl acetate yielding **160** as colourless plates (0.33g, 25% based on expected product) with mp: 90 -4°C. Tlc showed one or two components.

ir (KBr disc): 2990, 1570, 1380, 1260, 1225, 1120.

ms: 207 (M^+).

^1H nmr: complex peaks at: 1.11, 1.17(t), 2.74, 2.78(q), 2.98, 3.04(s),

3.21, 3.71 (multiplets typical of morpholino residue) and 5.03.

Preparation of 1-methylsulphonyl-1-methylthiobutan-2-one, **129** (R=Me)

N-methylthiophthalimide (2.57g, 0.0171 moles), **128**, (2.55g, 0.017 moles), triethylamine (25ml) and methylene chloride (150ml) were stirred under dry nitrogen for 72 hours. The solution was acidified with HCl and then the methylene chloride was dried and evaporated *in vacuo*. The resulting solid was shaken with petrol (5 x 50ml), the soluble fraction was removed and evaporated yielding a white solid **129** (R=Me) (3.16g, 94%) which was recrystallised from a small quantity of petrol, yielding colourless needles of **129** (R=Me), mp: 47-9°C.

ir (KBr disc): 2970, 2915, 1715, 1380, 1320, 1105, 1050, 960:

ms: 196 (10, M^+), 139 (5), 118 (7), 117 (52), 89 (72), 88 (10), 79 (6), 64 (16), 63 (17), 61 (52), 60 (18), 59 (13), 58 (9), 57 (64), 55 (6), 49 (12), 47 (100).

^1H nmr ($CDCl_3$): 1.12 (t,3H),
2.43 (s,3H,MeS),
2.83 (q,2H),
3.12 (s,3H,$MeSO_2$).
4.49 (s,1H).

^{13}C nmr: 7.22 (q),
16.65 (q),
36.58 (t),
36.86 (q),
73.87 (t),
200.19 (s,C=O).

Preparation of bisalkylsulphenylated long-chain containing β-ketosulphones, **132**

A mixture of a N-alkylthiophthalimide (0.012 mol), triethylamine (20ml) and a long-chain containing β-ketosulphone (0.006 mol) in methylene chloride (50ml) was stirred under an atmosphere of dry nitrogen for fourteen hours. The solution was then washed with hydrochloric acid (2 x 50ml, 10%) and water (2 x 50ml) and the organic layer was dried. On evaporation under reduced pressure a white solid remained which was recrystallised from methanol yielding **133** (90-95%) as a finely crystaline white powder.

For **132**: (R=Me,n=12)$CH_3(CH_2)_{12}COC(SMe)_2SO_2Me$ mp: 34-6°C

For **132**: (R=Et,n=14) $CH_3(CH_2)_{14}COC(SEt)_2SO_2Me$ mp: 35-6°C

^{13}C nmr ($CDCl_3$): 13.46 (2C), 13.93, 22.51, 24.16, 26.47, 28.88, 29.21 (2C)*, 29.48 (5C),* 31.75, 38.11, 38.57, 199.68.

For **132**: (R=Me,n=14) $CH_3(CH_2)_{14}COC(SMe)_2SO_2Me$ mp: 38-9°C

^{1}H nmr ($CDCl_3$): 0.88 (t, 3H), 1.26-1.73 (br s), 2.35 (s, 6H), 3.01 (t, 2H), 3.22 (s, 3H).

^{13}C nmr ($CDCl_3$): 13.93, 14.70 (2C), 22.51, 24.09, 28.89, 29.22 (2C),* 29.49 (7C),* 31.76, 38.12, 38.83, 199.44.

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*The number of carbons in these resonances is an estimate and is not noted in the carbon-13 spectra of similar compounds described consequently.

Preparation of monoalkylsulphenylated long-chain β-ketosulphones, 131

A mixture of ethane thiol (0.4ml, 0.0054 mol) and a bissulphenylated β-ketosulphone, 132, (0.0025 mol) were stirred under an atmosphere of dry nitrogen in tetrahydrofuran (50ml) to which an excess of pre-washed sodium hydride (0.45g, 0.0094 mol), 50% dispersion in oil) had been added. After four hours the reaction mixture was poured into water (30ml) and acidified carefully with concentrated hydrochloric acid. Extraction of this mixture with methylene chloride (3 x 40ml) followed by drying of the organic layer and evaporation yielded a white solid. Recrystallisation from petroleum ether or methylene chloride-petroleum ether yielded a fine white microcrystalline solid in 95-98% yield.

For 131 (R=Me, n=12), $CH_3(CH_2)_{12}COCH(SMe)SO_2Me$: mp: 62-4°C

ir (KBr disc): 2960, 2920, 1720, 1360, 1320.

^1H nmr ($CDCl_3$): 0.89 (t,3H), 1.26 (br;22H), 2.41 (t,2H), 2.73 (s,3H), 3.10 (s,3H), 4.46 (s,1H).

^{13}C nmr ($CDCl_3$): 13.98, 16.79,

22.56, 23.04,
28.64, 29.22,
29.49, 31.78,
36.70, 43.63,
74.10, 198.46.

For **131**(R=Me,n=14) $CH_3(CH_2)_{14}COCH(SMe)SO_2Me$: mp: 77-9°C

For **131**(R=Et,n=14) $CH_3(CH_2)_{14}COCH(SEt)SO_2Me$: mp: 49-51°C

^{13}C nmr ($CDCl_3$): 13.95, 22.55,
23.13, 27.71,
28.62, 29.23,
29.51, 31.77,
36.68, 43.31,
72.02, 199.05.

Oxidation of monosulphenylated β-ketosulphones, **134**, **135**, **164**.

A mixture of the monosulphenylated β-ketosulphones (0.005 mol) and meta-chloroperoxybenzoic acid (>3 mol eq, excess) in methylene chloride (80ml) was stirred under a dry nitrogen atmosphere for five hours. Evaporation to approximately half the volume yielded a white solid which was filtered off. Addition of petrol to the remaining solution then precipitated another solid which was recrystallised further from methylene chloride-petroleum ether yielding colourless plates of the corresponding bissulphone in 85-95% yield.

For 134: mp: 128-30°C

ms: 228(8), 199(7), 160(9), 150(33), 138(12), 121(34), 105(18), 104(31), 103(18), 89(6), 81(7), 80(40), 79(58), 76(42), 75(11), 74(12), 65(39), 64(33), 63(45), 58(46), 57(100), 55(32), 50(28).

^{1}H nmr ($CDCl_3$): 1.16 (t,3H), 2.86 (q,2H), 3.33 (s,6H), 5.38 (s,exch,1H).

^{13}C nmr ($CDCl_3$: 7.06 (q), 40.72 (t), 41.65 (q), 85.73 (d), 194.14 (s).

For:

135(R=Et,n=14) $CH_3(CH_2)_{14}COCH(SO_2Et)SO_2Me$ mp: 97.5-100°C

135(R=Ph,n=10) $CH_3(CH_2)_{10}COCH(SO_2Ph)SO_2Me$ mp: 116-119°C

135(R=Me,n=14) $CH_3(CH_2)_{14}COCH(SO_2Me)SO_2Me$ mp: 116-118°C

^{1}H nmr (d_6-DMK): 0.88 (t, 3H), 1.19-1.77 (br s), 2.83 (t, 2H), 3.36 (s, 6H).

135(R=Ph,n=16) $CH_3(CH_2)_{16}COCH(SO_2Ph)SO_2Me$ mp: 117-119°C

^{13}C nmr (d_6-DMK): 13.93, 22.51, 28.63, 29.50, 31.76, 37.52, 43.53, 129.50, 130.02, 135.44, 191.19.

135(R=Ph,n=12) $CH_3(CH_2)_{12}COCH(SO_2Ph)SO_2Me$ mp: 112-116°C

ms: 444 (1, M^+), 366 (13), 365 (52), 333 (4), 305 (9), 304 (50), 277 (10), 225 (17), 224 (56), 223 (93), 222 (10), 212 (17), 211 (100), 206 (22), 205 (53), 150 (20), 143 (21), 141 (63), 137 (45), 135 (23), 133 (11), 126 (17), 124 (74), 122 (17), 120 (21), 110 (26), 109 (20), 108 (30), 106 (12), 97 (20), 96 (52), 95 (40), 91 (14), 85 (38), 84 (17), 83 (47), 82 (15), 81 (37), 79 (23), 78 (28), 77 (91),

73 (18), 71 (70), 69 (56), 67 (26).

A CHS elemental analysis agreed with an empirical formula of $C_{22}H_{36}O_5S_2$ (expected 59.46% C, 8.11% H and 14.41% S; observed 59.45% C, 8.32% H and 14.53% S).

For **164** $PhCOCH(SO_2Me)_2$ mp: 196-7°C, tit. 195-6.[272]

^1H nmr ($CDCl_3$): 3.41 (s,6H), 6.11 (s,1H), 7.30-8.10 (m,5H),

^{13}C nmr (d_6-DMK): 41.39 (q,2C), 82.07 (d), 129.04 (d,2C), 129.32 (d), 129.81 (d,2C), 134.38 (s), 188.26 (s).

Preparation of benzoylmethyl-1-(4-chlorobutyl)-sulphone, **153**.

Sodium hydride (0.423g, 50% suspension in oil, 0.0088 mol) was scrupulously washed with dry petroleum ether, to remove the oil, and then dried under reduced pressure. A solution of **106** (1.74g, 0.0088 mol) in tetrahydrofuran (25ml) was then added to the dry gray

solid and the resulting mixture was stirred at 0°C under dry nitrogen for thirty minutes. To this solution of the mono anion of **106** was added n-butyl lithium (4ml, 2.2M solution in hexane, 0.0088 mol) producing a yellow solution. 1-Bromo-3-chloropropane (0.87ml, 0.0088 mol) in tetrahydrofuran (2ml) was then added dropwise and the resulting mixture was stirred at 0°C for a further three hours and then allowed to warm up to room temperature. After filtration, to remove the precipitated inorganic salts, the mixture was acidified with hydrochloric acid, extracted with methylene chloride (4x20ml), dried with magnesium sulphate and evaporated to dryness *in vacuo*.

The resulting residue was triturated with petroleum ether, to remove any unreacted alkyl halide and the remaining off-white solid was recrystallised from methanol. The product, **153**, formed microcrystals with mp: 97.5-98.5°C in overall yield 79% (1.9g)

This procedure was successfully repeated on a ten times scale with a resulting 81% yield.

ir (KBr disc): 2970, 2930, 1690, 1340, 1330, 1140.

ms: 276 (0.3, M+2), 274 (1, M^+), 239 (8), 120 (43), 106 (15), 105 (100), 77 (31), 55 (27), 51 (15).

^{1}H nmr ($CDCl_3$): 1.8-2.2 (m,2H), 3.30 (t,3H), 3.57 (t,2H), 4.57 (s,2H), 7.4-8.1 (m,5H).

^{13}C nmr ($CDCl_3$): 19.40, 30.80, 43.76, 52.75, 59.53, 128.92, 129.18, 134.66, 135.67, 189.11.

Preparation of benzoylmethyl-1-(4-iodobutyl)-sulphone, **154**.

A mixture of **153** (5.17g, 0.019 mol) and sodium iodide (3.0g, slight excess) was refluxed in acetone (200ml) for three hours. The resulting two-phase mixture was cooled and then evaporated to dryness on a rotary evaporator. The residue was triturated with methylene chloride and the yellow organic layer was washed with sodium thiosulphate solution (20ml, 5%), dried with magnesium sulphate and evaporated in a flask protected from light. The crude product was recrystallised from methanol yielding a 93% yield (6.4g) of fine colourless crystals of **154** with mp: 99-101°C.

ir (KBr disc): 2960, 2920, 1685, 1595, 1330, 1130, 1120.

ms:	366 (0.2,$M^{+\cdot}$), 240 (10), 239 (50), 120 (37), 106 (13), 105 (100), 103 (29), 91 (34), 78 (11), 77 (32), 65 (16), 55 (23), 51 (12).
^{1}H nmr ($CDCl_3$):	1.8-2.2 (m,4H), 3.0-3.6 (m,4H), 4.55 (s,2H), 7.4-8.1 (m,5H).
^{13}C nmr ($CDCl_3$	19.43, 22.99, 31.60, 43.67, 59.64, 128.90, 129.11, 134.52, 135.70, 189.11.

Preparation of 2-benzoylthiane-1,1-dioxide, 155.

A: 'Traditional conditions'.

Sodium hydride (0,17g, 50% suspension in oil, 0.0035 mol) was washed thoroughly with petroleum ether, to remove the oil, and then dried in vacuo. To this dried powder was added a solution of **154** (1.25g, 0.0034 mol) in dry dimethyl sulphoxide (55ml) and the resulting mixture was stirred for four hours under dry nitrogen. After this time the reaction mixture was poured into iced water (30ml), acidified with 1M HCl and extracted with methylene chloride (3x35ml). The combined

organic layers were washed with copious quantities of water to remove any residual DMSO, and then evaporated to dryness on a rotary evaporator. The crude product was recrystallised from ethyl acetate which produced colourless needles of **155** with mp: 139-141°C, yield 86%.

If tetrahydrofuran was used in place of DMSO then a much lower yield of **155** was realised.

B:Phase transfer conditions.

A mixture of **154** (0.18g, 0.00049 mol) and ethylhexadecyldimethyl ammonium bromide (0.15g, catalyst) was dissolved in methylene chloride (5ml). To this was added sodium hydroxide (0.02g, 0.0005 mol) in water (8ml). The resulting two-phase mixture was stirred vigorously until the pH of the aqueous layer was about 7 (approx. one hour). The two layers were then separated and the volume of the organic layer was increased to 20ml by addition of methylene chloride. This was washed with water (3x20ml), sodium thiosulphate solution (2x25ml, 5%) and saturated sodium chloride solution (20ml). The organic layer was dried with $MgSO_4$ and evaporated to dryness *in vacuo*. The resulting off-white solid was recrystallised several times from ethyl acetate yielding colourless needles of **155** (0.11g, 90%) with mp: 139-140°C.

This procedure was repeated on a larger scale (15x) with a resulting yield of 85% of **155** after recrystallisation from methanol.

ir (KBr disc):	2960, 2930, 1670, 1595, 1580, 1450, 1360, 1335, 1290, 1270, 1250, 1220, 1165, 1120, 1070, 1000, 930, 850, 785, 730, 715, 680, 655, 550.
ms:	238 (13, M^+), 106 (9), 105 (100), 77 (21).
^1H nmr ($CDCl_3$):	see text.
^{13}C nmr ($CDCl_3$):	20.34, 24.10, 28.20, 51.44, 65.09, 128.87, 134.22, 135.72, 192.20.

Preparation of 2-benzoyl-2-chlorothiane-1,1-dioxide, **156**.

Sodium hydride (0.0263g, 0.00055 mol, 50% suspension in oil) was washed with dry petroleum ether to remove the oil and then dried *in vacuo*. To this was added a solution of **156** (0.1308g, 0.00055 mol) in tetrahydrofuran (6ml). The mixture was stirred at room temperature under an atmosphere of dry nitrogen for 30 minutes during which time the rapid evolution of

hydrogen ceased. To this two-phase mixture was added N-chlorosuccinimide (0.0734g, 0.00055 mol) in one batch and a further portion of THF (6ml) was added. This was then refluxed under dry nitrogen for one and a half hours, cooled, poured into water (10ml) and extracted with methylene chloride (3x15ml). The organic layer was then evaporated and the residue was dissolved in ether (50ml), washed with saturated sodium chloride solution (2x25ml) and dried with anhydrous magnesium sulphate. Upon evaporation to dryness in a vacuum a yellow residue remained which consisted of a mixture of compounds with approximately 85% conversion to **156** (based on data from an integrated nmr spectrum).

This mixture was separated by vacuum-assisted column chromatography using silica gel as stationary phase and methylene chloride as eluant, as described above. Compound **156** was recovered in a pure state and was recrystallised from ethyl acetate-petroleum ether giving a 74% yield, based on starting materials used.

Halogenation was attempted by several other methods all of which failed: SO_2Cl_2 with and without reflux, with and without triethylamine, bromine with and without triethylamine, N-chlorosuccinimide with and without reflux.

ir (KBr disc): 2960, 2940, 2920, 1690, 1600, 1580, 1450, 1430,

1405, 1320, 1295, 1235, 1180, 1145, 1135, 1060, 1050, 1015, 940, 920, 850, 825, 790, 740, 720, 700, 695, 660, 560, 530, 500, 480.

ms: 274 (1.5, M+2), 272 (4, M^+), 237 (1), 106 (10), 105 (100), 77 (21), 51 (8).

^{1}H nmr ($CDCl_3$): 1.8-2.1 (m, 4H), 2.5-3.5 (m, 4H), 7.3-8.5 (m, 5H).

^{13}C nmr ($CDCl_3$): 19.72, 23.77, 37.41, 49.77, 85.21, 127.90, 130.86, 133.45, 189.79.

Preparation of 2-chlorothiane-1,1-dioxide, 157.

To **156** (0.0914g, 0.000335 mol) was added potassium hydroxide (0.03, excess) in 95% ethanol (10ml). This mixture was refluxed for two hours and then evaporated to dryness in vacuo. The resultant residue was triturated with methylene chloride and the organic

layer * was dried with $MgSO_4$ and evaporated yielding **157** in 94% yield (0.056g) which was recrystallised from methylene chloride and pentane to give colourless needles (mp: 72-73°C, lit. 74°C).[273] A mixed melting point with an authentic sample of **157** gave an identical melting point range.

ir (KBr disc):	2970, 2960, 2935, 1320, 1300, 1165, 1135.
ms:	170 (4,M+2), 168 (11,M^+), 133 (22), 105 (17), 103 (50), 77 (14), 76 (23), 75 (36), 69 (16), 68 (22), 67 (54), 55 (31), 42 (100), 41 (82), 40 (75).
^1H nmr ($CDCl_3$):	see text.
^{13}C nmr ($CDCl_3$):	19.70, 23.66, 33.40, 48.11, 70.23.

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*The residue was dissolved in aqueous acid, extracted with methylene chloride, dried and evaporated. The residue was recrystallised from water and shown to be benzoic acid by ir, nmr and a mixed melting point with an authentic sample.

Preparation of thiane-1,1-dioxide, 158.

To 2-benzoylthiane-1,1-dioxide, 155 (1.8g, 0.0049 mol) was added potassium hydroxide (0.27g, 0.0049 mol) in ethanol (50ml). The mixture was refluxed for two hours and then rotary evaporated. The residue was extracted with methylene chloride (2 x 25ml), the organic layer was washed with water (25ml), dried with magnesium sulphate and rotary evaporated to dryness. Recrystallisation from ethanol-water yielded 0.62g (94%) of the desired sulphone with a melting point 97-8°C (lit. 98.5-99°C)[271] which was undepressed when mixed with an authentic sample.

Preparation of 2-chloro-2-methylsulphonyl-1-phenylethanone, 112

A solution of 2-methylsulphonyl-1-phenylethanone (5g, 0.025 mol) in dry THF (80ml) was added to dry sodium hydride (1.21g, 0.025 mol of 50% suspension in oil) which had been washed with petroleum ether. The mixture was stirred at room temperature under dry nitrogen for one hour during which time the rapid evolution of hydrogen ceased. To this two-phase mixture was added N-chlorosuccinimide (3.38g, 0.025 mol) in several small portions followed by dry tetrahydrofuran (20ml). The mixture was refluxed for 90 minutes under dry nitrogen, cooled and poured into ice-water (20ml)

and extracted with methylene chloride (3 x 25ml). The organic layer was then washed with water (2 x 25ml), dried with magnesium sulphate and evaporated to dryness *in vacuo*. The crude solid was recrystallised from ether yielding 4.1g (71%) of **112** as colourless needles with mp: 102-103°C (lit. 103-4,°C).[73]

ir (KBr):	3040, 3015, 2980, 2940, 1680, 1585, 1315, 1130.
^{1}H nmr ($CDCl_3$):	3.20 (d,J=0.7Hz,3H), 5.96 (q,J=0.7Hz,1H), 7.5-8.1 (m,5H).
^{13}C nmr ($CDCl_3$):	36.76 (q), 68.21 (d), 128.92 (d,2C), 129.35 (d,2C), 133.76 (s), 135.09 (d), 187.26 (s,C=O).

Preparation of 2-bromo-2-methylsulphonyl-1-phenylethanone **113**.

This compound was prepared according to the published procedure.[73] The product, after recrystallisation from methylene chloride-petrol, was obtained in 90% yield as colourless needles with mp: 90-91°C. lit. 90-91°C,[73]

^1H nmr ($CDCl_3$):	3.30 (s,3H),
	6.10 (s,1H),
	7.5-8.1 (m,5H).
^{13}C nmr ($CDCl_3$):	37.58 (q),
	55.82 (t),
	128.98 (d,2C),
	129.14 (d,2C),
	133.59 (s),
	134.87 (d),
	187.58 (s,C=O).

Preparation of 2-methylsulphonyl-2-methylthio-1-phenylethanone **162**.

A solution of N-methylthiophthalimide (1.93g, 0.01 mol). 2-methylsulphonyl-1-phenylethanone (1.98g, 0.01 mol) and triethylamine (2ml, excess) in methylene chloride (80ml) was stirred overnight, at room temperature, under dry nitrogen. After this time the solution was cooled and filtered and the mother liquor was then washed with HCl (2 x 4ml, 1M) and water (2 x 30ml), dried with sodium sulphate and evaporated to dryness under vacuum. The orange-yellow solid was triturated with petroleum ether and then recrystallised from methanol yielding 2.21g (90%) of the required product, **162** as colourless needles, mp: 115-117°C.

^1H nmr ($CDCl_3$):	2.84 (s,3H),
	3.28 (s,3H),
	5.39 (s,1H),
	7.5-8.2 (m,5H).
^{13}C nmr ($CDCl_3$):	16.75 (q),
	36.92 (q),
	70.23 (d),
	128.92 (d,),
	134.60 (d),
	189.78 (s,C=O).

Preparation of 2-ethylthio-2-methylsulphonyl-1-phenylethanone **114**.

A mixture of 2-methylsulphonyl-1-phenylethanone (2g, 0.01 mol), N-ethylthiophthalimide (2.09g, 0.01mol) and triethylamine (2ml, excess) in dry methylene chloride (100ml) was stirred for 14 hours at room temperature under an atmosphere of dry nitrogen. After this time the solution was cooled in an ice-bath and filtered to remove the precipitated phthalimide. The organic layer was washed with HCl (2 x 25ml,1M) and water (2 x 25ml), dried with magnesium sulphate and evaporated *in vacuo*. Recrystallisation of the solid residue from methanol yielded 2.2g (85%) of **114** as colourless needles with mp: 150-2°C.

^{1}H nmr ($CDCl_3$): 1.32 (t,3H),
3.03 (q,2H),
3.25 (s,3H),
5.40 (s,1H),
7.15-8.3 (m,5H).

^{13}C nmr ($CDCl_3$): 14.86 (q, $\underline{C}H_3CH_2$-),
27.82 (t, $CH_3\underline{C}H_2$-),
36.78 (q,$\underline{C}H_3SO_2$-),
68.44 (d,-CO$\underline{C}$H(SEt)SO_2-),
128,91 (d,4C),
134.51 (d),
184.78 (s,$\underline{C}$=O).

Preparation of 2-methylsulphonyl-1-phenyl-2-propanone, 165.

A solution of 2-methylsulphonyl-1-phenylethanone (2g,0.01 mol) and methyl iodide (4.5g, 0,03, excess) in methylene chloride (25ml) was stirred vigorously. A mixture of ethylhexadecyldimethylammonium bromide (3.75g, 0.01 mol) and sodium hydroxide (0.4g, 0.01 mol) in water (25ml) was added and the two-phase mixture was stirred until the aqueous layer was neutral to pH indicator paper. The layers were separated and the aqueous layer was extracted with methylene chloride (25ml). The combined organic layers were washed with water, dried with magnesium sulphate and evaporated

yielding an off-white solid (2.0g, 94%). The solid was recrystallised twice from ethyl acetate-petrol and then chromatographed using the vacuum technique described above with methylene chloride as eluant. Pure 2-methylsulphonyl-1-phenylpropanone (1.4g, 66%) was thus obtained. mp: 54-5°C (lit. 56-57.5).[123]

ms: (70eV): 212 (6, $M^{+\cdot}$), 132 (9), 115 (7), 105 (100, $PhCO^{+}$), 77 (35).

^1H nmr ($CDCl_3$): 1.68 (d,3H), 2.93 (s,3H), 5.02 (q,1H), 7.3-8.2 (m,5H).

Preparation of 1-phenyl-2-phenylsulphonylethanone, **166**.

A mixture of α-chloroacetophenone (2g, 0.013 mol) and sodium benzenesulphinate dihydrate (2.6g, 0.013 mol) in ethanol (200ml) was refluxed under nitrogen for 16 hours. The solution was cooled to room temperature and evaporated *in vacuo*. The residue was then dissolved in methylene chloride and washed with water (2 x 50ml), dried with magnesium sulphate and rotary evaporated. The slightly yellowish solid was recrystallised from toluene yielding 3.21g (95%) of **166** as colourless needles. mp: 92-3°C, lit. 90-1°C.[187]

^{1}H nmr ($CDCl_3$): 4.17 (s,2H),
7.2-8.1 (m,10H).

^{13}C nmr ($CDCl_3$): 63.27 (t),
128.37 (d,2C),
128.65 (d,2C),
129.03 (d,4C),
133.99 (d, para C),
134.12 (d, para C),
135.63 (s),
138.74 (s),
187.80 (s,C=O).

Preparation of 1-phenylsulphonyl-1-phenylthio-propan-2-one, **172**.

The procedure was as for the preparation of **129**, except that 1-phenylsulphonyl-propan-2-one and N-phenylthiophthalimide were used as starting materials. The yield was 86% and the product **172** was recrystallised from ethanol-water, yielding colourless needles, mp: 68-9°C.

^{1}H nmr ($CDCl_3$): 2.47 (s,3H,MeCO),
4.78 (s,1H),
7.20 (br s,5H,PhS),
7.3-8.1 (m,5H).

Preparation of chloromethyl-methylsulphone, **178**

A solution of potassium hydroxide (1g, 0.018 mol) in 95% ethanol (50ml) was added to 2-chloro-2-methylsulphonyl-1-phenylethanone (4.1g, 0.018mol). The mixture was refluxed for two hours and then evaporated to dryness using a rotary evaporator. The resulting residue was extracted into methylene chloride which was dried and evaporated to yield 1.8g, (77%) of chloromethyl methyl sulphone after recrystallisation from ether-petrol. mp: 54-6°C (lit. 57.2-58.2).[73]

^{1}H nmr ($CDCl_3$): 3.10 (s,3H),
4.48 (s,2H),

^{13}C nmr ($CDCl_3$): 37.40 (q),
56.60 (t).

The methylene chloride insoluble material, after evaporation. was acidified with concentrated HCl, extracted with methylene chloride, dried with magnesium sulphate and evaporated to yield 2.0g (91%) of benzoic acid which was identified by its melting point (121-2°C) and its ^{1}H nmr spectrum.

Preparation of bromomethyl methyl sulphone, **181**.

This compound was prepared in exactly the same way as was chloromethyl methyl sulphone **178**. Recrystallisation from ether yielded 75% of small needles with mp: 33-35°C, lit. 34°C.[73]

^{1}H nmr ($CDCl_3$): 3.13 (s,3H),
4.45 (s,2H).

^{13}C nmr ($CDCl_3$): 37.75 (q),
42.35 (t).

An almost qualitative yield (94%) of benzoic acid was again obtained by work-up of the organic insoluble fraction after evaporation.

Preparation of benzyl methyl sulphone **183**.

A solution of benzyl methyl sulphide (1.0g, 0.007 mol) and ammonium molybdate (0.5g) in methanol (20ml) was stirred. Hydrogen peroxide (10ml, 30%, excess) was added dropwise so as to keep the temperature below 40°C. After stirring for eight hours the solvent was evaporated and the residue was extracted into ether. The ether solution was washed with water and saturated sodium chloride solution and then dried with magnesium sulphate. Rotary evaporation of the solvent gave 1.1g (89%) of the expected sulphone which was recrystallised from methylene chloride-petrol giving a mp: 120-1°C, lit. 119-20°C.[274]

^{1}H nmr ($CDCl_3$): 2.70 (s,3H),
4.20 (s,2H),
7.30 (s,5H).

^{13}C nmr ($CDCl_3$): 38.50 (q),
60.70 (t),

127.85 (s),
128.55 (d,3C),
127.85 (d,2C).

Preparation of dibenzyl sulphone, **185**.

Dibenzylsulphone, **185**, was prepared as for **183** except that dibenzyl sulphide was used. Recrystallisation yielded 2.2g (99%) of the desired sulphone; mp: 145-6°C lit. 151°C.[275]

^{1}H nmr ($CDCl_3$): 4.0 (s,2H),
7.2 (s,5H).

^{13}C nmr ($CDCl_3$): 57.84 (t),
127.40 (s),
128.80 (d,2C,m-ArC),
130.70 (d,3C,o,p-ArC).

Preparation of benzyl α-chlorobenzyl sulphone, **186**.

A solution of benzyl α-chlorobenzyl sulphide (2g, 0.008 mol) in dry ether (25ml) was cooled to 0°C in an ice-bath. To this solution, m-chloroperbenzoic acid (3.5g, excess) in ether (25ml) was added dropwise so that the temperature stayed below 5°C. The mixture was stirred for three hours after which time it was washed with sodium bisulphite solution (20ml, 5%), aqueous sodium bicarbonate solution (3 x 20ml, 2.5%), water

(25ml) and then saturated sodium chloride solution (25ml). Evaporation under vacuum, after drying, yielded a mixture of compounds which were separated by preparative tlc using silica gel and methylene chloride-petrol as eluant. Recrystallisation from this same solvent mixture yielded 1.5g (67%) of the desired chlorosulphone, mp: 117-8°C, lit. 116-7°C.[276]

^{1}H nmr ($CDCl_3$): 4.25 (AB pattern, J=14Hz), 5.33 (s,1H), 7.25 (br s,10H).

^{13}C nmr ($CDCl_3$): 55.91 (t), 70.45 (d), 126.92 (s), 128.31 (s).

Preparation of diethyl sulphone, 189.

Diethyl sulphide (10ml, 0.09 mol) and ammonium molybdate (0.5g) were dissolved in methanol (50ml) the resulting solution was stirred magnetically whilst hydrogen peroxide (50ml, 30%, excess) was added dropwise, the temperature being kept below 40°C. After stirring at room temperature overnight the solvent was evaporated and the resulting solid was extracted using methylene chloride (4 x 25ml). After washing the organic layer with sodium bisulphite solution (to remove any residual hydrogen peroxide) and then water, the organic

layer was dried and evaporated yielding 10.2g (93%) of diethyl sulphone mp: 72-3°C, lit. 73-4°C.[269]

^{13}C nmr ($CDCl_3$): 5.93 (q),
45.57 (t).

Preparation of 2-carbomethoxy-N-methylpyrrole

The title compound was prepared in a two-step procedure from pyyrole-2-carboxaldehyde using the procedure of Hodge and Rickards.[277]

^{13}C nmr ($CDCl_3$): 36.28 (q,N<u>Me</u>),
50.51 (q,CO_2<u>Me</u>),
107.46 (d,C-4),
117.42 (d,C-3),
121.96 (s,C-2),
129.10 (d,C-5),
161.32 (s,<u>C</u>=0).

Preparation of 2-(N-methylpyrrole)sulphonyl-methylsulphonylmethane, **136**.

2-Carbomethoxy-N-methylpyrrole (0.01 mol) was added to a solution of the monoanion from dimethyl sulphone (0.01 mol) as made in preparation of **106**. Work-up using this same procedure and recrystallisation from methanol yielded **136** (89%) as very long, colourless needles, mp: 115-116°C.

ir (KBr disc): 3110, 3020, 3000, 2970, 1635, 1520, 1460, 1420, 1380, 1300, 1250, 1210, 1145, 1120, 1100, 1070, 960, 900, 800, 745, 675, 645, 580.

ms: 202 (7,M+1), 201 (66,M^+), 123 (5), 122 (47), 121 (7), 109 (7), 108 (100), 94 (28), 80 (11), 51 (14).

^{1}H nmr ($CDCl_3$): 3.20 (s,3H), 3.83 (s,3H), 5.13 (s,1H), 6.00 (dd, J=2,5 Hz,1H), 6.72 (m,2H), 7.05-7.6 (m,5H).

^{13}C nmr ($CDCl_3$): 37.59 (q), 41.67 (q), 62.09 (t), 109.23 (d,C-4), 122.82 (d,C-3), 129.93 (s,C-2), 133.78 (d,C-5), 177.20 (s,C=0).

Preparation of pyridyl β-ketosulphones **137** and **138**.

These compounds were prepared using ethyl nicotinate and ethyl isonicotinate as the starting esters respectively. Reaction conditions were as for preparation of **106** except that THF was used as solvent. Work-up consisted of acidifying the reaction mixture with concentrated hydrochloric acid followed by evaporation to dryness *in vacuo* of the resulting solution. The residue remaining was heated with a hot air gun under vacuum to remove the dimethyl sulphone by sublimation. Recrystallisation of the remaining residue from a small quantity of water yielded 2-methylsulphonyl-1-(3-pyridyl)-ethanone, **137** or 2-methylsulphonyl-1-(4-pyridyl)-ethanone **138** in 57% and 41% yield respectively. Better crystals (broad spars) of **138** were produced by further recrystallisation from methylene chloride. For **137** mp: 83-4°C, for **138** mp: 111-112°C.

For **137**: ir (KBr disc): 3010, 2950, 2920, 1680, 1580, 1430, 1310, 1280, 1140, 1040, 1000, 960, 900, 830, 790, 750, 700.

ms: 199 (15, $M^{+\cdot}$), 184 (2), 137 (5), 136 (33), 122 (4), 121 (4), 107 (7), 106 (100), 92 (5), 79 (11), 78 (42),

65 (7), 51 (8).

^{1}H nmr ($CDCl_3$): 3.16 (t,3H,J=0.7Hz), 4.62 (q,2H,J=0.7Hz), 7.49 (dd,J=4.7,7.9Hz), 8.30 (dt,J=1.5,8Hz), 8.86 (dd,J=1.4,4.6Hz), 9.22 (d,J=1.5Hz).

^{13}C nmr ($CDCl_3$): 41.71 (q), 61.21 (q), 123.66 (d), 136.44 (d), 150.17 (d), 154.33 (d), 170.14 (s), 176.81 (s).

For **138**: ir (KBr disc): 3010, 2980, 2920, 1700, 1550, 1410, 1335, 1315, 1295, 1200, 1160, 1120, 1000, 970, 900, 830, 810, 775, 700, 645.

ms: 201 (5,M+2), 200 (6,M+1), 199 (60,M^+), 121 (3), 107 (9), 106 (100), 92 (5), 79 (19), 78 (46), 65 (10), 51 (28).

^{1}H nmr ($CDCl_3$): 3.06 (s,3H), 4.51 (s,2H), 7.55, 8.59 (AA'BB' pattern, 4H).

^{13}C nmr ($CDCl_3$): 41.66, 61.18, 121.40, 151.14, 189.06.

Reaction of **137** and **138** with N-phenylthiophthalimide.

Reaction conditions were as for preparation of **172**. Yields of the triethylammonium salts **141** and **142** were 86% and 79% respectively.

For **142** mp: 98°C (decomp.).

A CHN elemental analysis agreed with an empirical formula of $C_{20}H_{28}N_2O_3S_2$ (expected 58.82% C, 6.86% H and 6.86% N; observed 58.92% C, 6.93% H and 6.80% N).

For **141** mp: 85-7°C (decomp.):

: 3000, 2980, 2660, 1570, 1490, 1470, 1395, 1340, 1300, 1260, 1150, 1115, 1060, 1015, 990, 950, 835, 815, 800, 750, 720, 700.

^1H nmr ($CDCl_3$): 1.15 (t,6H), 3.04 (q,4H), 3.11 (s,3H), 7.0-8.5 (m,9H).

^{13}C nmr ($CDCl_3$): 8.50 (q), 41.98 (br),

45.86 (t),
92.42 (br),
121.25,
124.51 (br),
128.44,
149.14,
186.14 (s),
189.41 (s).

Crystal data:

$(C_{14}H_{12}NO_3S_2)^-$ $(NHEt_3)^+$, triclinic, a=8.882(4), b=9.175(5), c=13.974(5) Å, α=97.56(4)°, β=91.09(3)°, γ=112.59(4)°, space group $P\bar{1}$, Z=2, D_c=1.31gcm^{-3}, Mo-Kα_1 radiation, λ=0.70926Å, μ=2.33cm^{-1}. 3857 unique reflections were collected of which 2427 had $I > 3\sigma(I)$ and were used. R=0.055.

Monosulphenylation of **136** to produce **139** or **140**.

Reaction with N-phenylthiophthalimide **111c** with **136** was carried out as for preparation of **172**. Reaction with N-methylthiophthalimide, **111a** with **136** was carried out as for preparation of **129**.

Preparation of **139** proceeded in 92% yield and recrystallisation from ethyl acetate-petroleum ether produced long colourless needles, mp: 97-8°C.

For **139** ms: 309 (7, M^+), 231 (9), 230 (60), 205 (5), 204 (15), 203 (100), 126 (9), 115 (7), 114 (9), 113 (59), 86 (5), 59 (10), 45 (10).

^1H nmr ($CDCl_3$): 2.50 (s,3H), 3.24 (s,3H), 3.94 (s,3H), 5.02 (s,1H), 6.22 (dd,1H,J=1.85,210Hz), 7.05 (m,5H).

^{13}C nmr ($CDCl_3$): 17.00 (q), 36.68 (q), 37.71 (q), 72.17 (d), 109.37 (d,C-4), 122.32 (d,C-3), 128.84 (s,C-2), 134.25 (d,C-5), 178.56 (s,C=0).

A CHN elemental analysis agreed with an empirical formula of $C_{14}H_{15}NO_3S_2$ (expected 54.37% C, 4.85% H and 4.53% N; observed 54.45% C, 4.94% H and 4.54% N).

For **140**:

mp:	126.5-128°C (colourless stout needles).
ir (KBr disc):	3100, 3005, 2980, 2965, 1735, 1620, 1525, 1480, 1455, 1405, 1380, 1300, 1250, 1185, 1110, 1065, 960, 945, 825, 760, 590,
^{1}H nmr ($CDCl_3$):	3.20 (s,3H), 3.83 (s,3H), 5.13 (s,1H), 6.00 (dd,J=2.0Hz, 5.0Hz), 6.72 (m,2H), 7.05-7.6 (m,5H).
^{13}C nmr ($CDCl_3$):	37.60 (q), 37.73 (q), 74.73 (d), 109.48, 122.37, 128.92 (s), 129.40 (3C), 132.25 (s), 133.70 (2C), 134.39, 178.88 (s).

Preparation of 2-methylsulphonyl-2-phenylthio-1-phenylethanone, **144**.

Reaction conditions as for preparation of **172** were used. **144** was obtained in 87% yield. mp: 99-100.5°C.

^{13}C nmr ($CDCl_3$): 37.68 (q), 72.69 (d), 128.89, 129.42, 129.59, 131.34 (s), 133.66, 134.48, 189.90 (s).

APPENDIX I

X-RAY DATA FOR **51**

Table XXI: Interatomic bond distances for 51

K	-K		3.872 (2)	S (2)	-O	(21)	1.438 (5)
K	-O	(22)	2.845 (5)	S (2)	-Me	(2)	1.754 (8)
K	-O	(22)	3.125 (5)	S (3)	-O	(31)	1.434 (5)
K	-O	(21)	2.818 (5)	S (3)	-O	(32)	1.437 (5)
K	-O	(31)	2.738 (5)	S (3)	-Me	(3)	1.757 (8)
K	-O	(32)	2.695 (5)	N	-C	(1)	1.323 (8)
K	-OH	(2)	2.860 (5)	N	-C	(5)	1.334 (8)
K	-OH	(2)	2.780 (5)	O (1)	-C	(1)	1.350 (8)
C	-S	(1)	1.718 (8)	O (1)	-Me	(1)	1.430 (1)
C	-S	(2)	1.718 (8)	C (1)	-C	(2)	1.400 (1)
C	-S	(3)	1.703 (8)	C (2)	-C	(3)	1.370 (1)
S (1)	-O	(11)	1.440 (5)	C (3)	-C	(4)	1.384 (9)
S (1)	-O	(12)	1.431 (5)	C (4)	-C	(5)	1.401 (9)
S (1)	-C	(4)	1.762 (6)	C (5)	-O	(5)	1.337 (8)
S (2)	-O	(22)	1.437 (5)	O (5)	-Me	(5)	1.438 (9)

Table XXII: Interbond angles for 51

K	-O (22)	-S (2)	144.8 (3)	C (3)	-C (4)	-C (5)	117.0 (1)
K	-O (22)	-S (2)	131.8 (3)	N	-C (5)	-C (4)	123.0 (1)
K	-O (21)	-S (2)	137.1 (3)	N	-C (5)	-O (5)	119.0 (1)
C	-S (3)	-O (31)	111.6 (3)	C (4)	-C (5)	-O (5)	118.0 (1)
C	-S (3)	-O (32)	107.0 (3)	C (5)	-O (5)	-Me(5)	118.0 (1)
C	-S (3)	-Me(3)	107.6 (4)	S (1)	-C	-S (2)	118.6 (5)
O (31)	-S (3)	-O (32)	115.7 (3)	S (1)	-C	-S (3)	120.0 (5)
O (31)	-S (3)	-Me(3)	107.1 (3)	S (2)	-C	-S (3)	120.9 (5)
O (32)	-S (3)	-Me(3)	107.5 (3)	C	-S (1)	-O (11)	111.3 (3)
K	-O (31)	-S (3)	133.4 (3)	C	-S (1)	-O (12)	107.4 (3)
K	-O (32)	-S (3)	135.1 (3)	C	-S (1)	-C (4)	108.0 (3)
C (1)	-N	-C (5)	118.0 (1)	O (11)	-S (1)	-O (12)	116.3 (3)
C (1)	-O (1)	-Me(1)	118.0 (1)	O (11)	-S (1)	-C (4)	105.1 (3)
N	-C (1)	-O (1)	119.0 (1)	O (12)	-S (1)	-C (4)	108.4 (3)
N	-C (1)	-C (2)	124.0 (1)	C	-S (2)	-O (22)	106.9 (3)
O (1)	-C (1)	-C (2)	117.0 (1)	C	-S (2)	-O (21)	111.1 (4)
C (1)	-C (2)	-C (3)	117.0 (1)	C	-S (2)	-Me(2)	109.1 (4)
C (2)	-C (3)	-C (4)	121.0 (1)	O (22)	-S (2)	-O (21)	116.7 (3)
S (1)	-C (4)	-C (3)	121.1 (5)	O (22)	-S (2)	-Me(2)	105.8 (3)
S (1)	-C (4)	-C (5)	121.7 (5)	O (21)	-S (2)	-Me(2)	107.0 (3)

Table XXIII: Atomic parameters (x 10^4, except x 10^3 for hydrogen and 10^5 for K and S(3)) for 51

Name	X/a	Y/b	Z/c	U_{iso}	Mod(U)
K	56178 (9)	33593 (21)	44839 (10)		4891 (82)
C	3202 (5)	414 (11)	3045 (5)		338 (43)
S(1)	2476 (1)	-1343 (3)	2614 (1)		373 (11)
O(11)	2833 (3)	-3209 (6)	2611 (3)		495 (26)
O(12)	1951 (2)	-1200 (6)	3133 (3)		507 (25)
S(2)	3345 (1)	1446 (3)	4132 (1)		390 (11)
O(22)	3990 (3)	2824 (7)	4323 (3)		560 (28)
O(21)	3443 (3)	-6 (7)	4849 (3)		632 (30)
Me(2)	2485 (4)	2796 (10)	4034 (5)		548 (43)
H(21)	1949 (4)	1909 (10)	3836 (5)	718(187)	
H(23)	2394 (4)	3929 (10)	3512 (5)	904(249)	
H(22)	2605 (4)	3430 (10)	4728 (5)	889(243)	
S(3)	38466 (9)	8844 (22)	24758 (11)		3916 (82)
O(31)	4674 (3)	843 (6)	3125 (3)		511 (26)
O(32)	3642 (3)	-422 (7)	1680 (3)		576 (29)
Me(3)	3647 (5)	3241 (9)	2012 (5)		607 (47)
H(31)	3044 (5)	3391 (9)	1481 (5)	844(347)	
H(32)	4084 (5)	3512 (9)	1688 (5)	924(281)	
H(33)	3733 (5)	4268 (9)	2581 (5)	1284(284)	
N	970 (3)	1217 (7)	217 (3)		372 (29)
O(1)	522 (3)	320 (7)	-1364 (3)		546 (30)
C(1)	978 (4)	-41 (9)	-440 (4)		406 (37)
Me(1)	76 (5)	2097 (12)	-1581 (5)		610 (50)

Table XXIII: (cont.)

Name	X/a	Y/b	Z/c	U_{iso}	Mod(U)
H(11)	-305 (5)	1995 (12)	-2328 (5)	1075(296)	
H(12)	447 (5)	3377 (12)	-1463 (5)	830(245)	
H(13)	-297 (5)	2179 (12)	-1158 (5)	917(249)	
C(2)	1451 (4)	-1710 (10)	-249 (4)		461 (39)
H(2)	1446 (4)	-2670 (10)	-813 (4)	797(229)	
C(3)	1922 (4)	-2061 (8)	685 (5)		414 (38)
H(3)	2310 (4)	-3317 (8)	866 (5)	671(200)	
C(4)	1910 (3)	-830 (9)	1403 (4)		366 (33)
C(5)	1429 (3)	831 (8)	1125 (4)		380 (35)
O(5)	1437 (3)	2092 (6)	1799 (3)		479 (26)
Me(5)	926 (5)	3767 (10)	1505 (5)		582 (45)
H(51)	1072 (5)	4536 (10)	2171 (5)	670(206)	
H(52)	282 (5)	3535 (10)	1187 (5)	1289(361)	
H(53)	1118 (5)	4608 (10)	1024 (5)	924(243)	
OH(2)	4625 (3)	-3298 (7)	3800 (3)		578 (28)

Table XXIV: Anisotropic temperature factors for 51

Name	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
K	5302 (84)	4323 (81)	5049 (82)	544 (69)	2729 (66)	153 (69)
C	373 (44)	283 (45)	358 (41)	-27 (35)	107 (35)	82 (35)
S(1)	435 (11)	296 (11)	386 (11)	57 (9)	145 (9)	13 (9)
O(11)	606 (28)	290 (23)	590 (27)	73 (20)	131 (22)	61 (20)
O(12)	496 (24)	525 (28)	501 (24)	78 (22)	256 (20)	-63 (22)
S(2)	427 (11)	433 (12)	309 (10)	3 (10)	146 (9)	71 (11)
O(22)	455 (25)	666 (32)	558 (27)	-224 (24)	207 (22)	-119 (23)
O(21)	945 (38)	592 (30)	359 (24)	134 (22)	284 (25)	254 (26)
Me(2)	581 (43)	505 (45)	557 (42)	-45 (35)	290 (35)	142 (34)
S(3)	4238 (84)	3545 (83)	3966 (78)	-282 (70)	2164 (67)	146 (67)
O(31)	424 (24)	560 (28)	549 (25)	-24 (23)	215 (21)	14 (22)
O(32)	600 (30)	540 (30)	588 (28)	-255 (23)	337 (24)	-106 (22)
Me(3)	824 (55)	391 (42)	606 (45)	183 (35)	378 (43)	136 (37)
N	409 (28)	353 (30)	355 (29)	5 (25)	131 (23)	43 (24)
O(1)	694 (34)	587 (32)	357 (25)	21 (22)	104 (24)	111 (25)
C(1)	363 (36)	444 (37)	412 (38)	-6 (31)	176 (30)	-50 (29)
Me(1)	623 (49)	740 (58)	467 (43)	143 (38)	138 (38)	156 (42)
C(2)	519 (38)	454 (41)	410 (37)	-64 (31)	187 (31)	10 (33)
C(3)	426 (37)	319 (37)	499 (41)	-60 (29)	176 (31)	13 (27)
C(4)	380 (34)	299 (33)	420 (34)	22 (27)	161 (28)	-35 (27)
C(5)	438 (35)	304 (34)	398 (37)	-16 (29)	199 (30)	-7 (29)
O(5)	622 (28)	393 (26)	421 (24)	-28 (21)	198 (22)	171 (21)
Me(5)	691 (50)	423 (42)	631 (44)	-32 (37)	279 (38)	225 (37)
OH(2)	821 (33)	429 (27)	486 (25)	-27 (22)	234 (24)	60 (29)

APPENDIX II

X-RAY DATA FOR 55

Table XXV: Interatomic bond distances for 55

S(1)	-O (11)	1.43 (1)	O(2)	-C (14)	1.360 (9)		
S(1)	-O (12)	1.43 (1)	O(2)	-Me (2)	1.464 (10)		
S(1)	-C (11)	1.73 (1)	O(3)	-C (26)	1.360 (9)		
S(2)	-O (21)	1.43 (1)	O(3)	-Me (3)	1.442 (10)		
S(2)	-O (22)	1.43 (1)	O(4)	-C (24)	1.367 (9)		
S(2)	-C (2)	1.73 (2)	O(4)	-Me (4)	1.42 (1)		
S(21)	-O (211)	1.41 (1)	C(11)	-C (12)	1.394 (10)		
S(21)	-O (212)	1.43 (1)	C(11)	-C (16)	1.415 (10)		
S(22)	-O (222)	1.43 (1)	C(12)	-C (13)	1.37 (1)		
S(22)	-C (220)	1.75 (1)	C(13)	-C (14)	1.39 (1)		
S(23)	-O (231)	1.43 (1)	C(14)	-C (15)	1.386 (10)		
S(23)	-O (232)	1.43 (1)	C(15)	-C (16)	1.372 (10)		
S(23)	-C (230)	1.75 (1)	C(21)	-C (22)	1.37 (1)		
S(3)	-O (31)	1.42 (1)	C(21)	-C (26)	1.410 (10)		
S(3)	-O (32)	1.42 (1)	C(22)	-C (23)	1.37 (1)		
S(3)	-C (3)	1.75 (2)	C(23)	-C (24)	1.38 (1)		
O(1)	-C (16)	1.361 (8)	C(24)	-C (25)	1.38 (1)		
O(1)	-Me (1)	1.447 (9)	C(25)	-C (26)	1.38 (1)		

Table XXVI: Interbond angles for 55

O(11)	-S	(1)	-O	(12)	119.3	(9)	S(1)	-C	(11)	-C	(16)	123.3	(7)
O(11)	-S	(1)	-C	(11)	111.1	(8)	C(12)	-C	(11)	-C	(16)	119.1	(6)
O(12)	-S	(1)	-C	(11)	109.0	(8)	C(11)	-C	(12)	-C	(13)	121.8	(6)
O(21)	-S	(2)	-O	(22)	119.6	(10)	C(12)	-C	(13)	-C	(14)	117.3	(7)
O(21)	-S	(2)	-C	(2)	109.0	(9)	O(2)	-C	(14)	-C	(13)	122.7	(6)
O(22)	-S	(2)	-C	(2)	108.2	(8)	O(2)	-C	(14)	-C	(15)	114.5	(6)
O(211)	-S	(21)	-O	(212)	119.8	(9)	C(13)	-C	(14)	-C	(15)	122.9	(6)
O(211)	-S	(21)	-C	(21)	109.9	(8)	C(14)	-C	(15)	-C	(16)	118.9	(6)
O(212)	-S	(21)	-C	(21)	108.7	(8)	O(1)	-C	(16)	-C	(11)	115.9	(6)
O(221)	-S	(22)	-O	(222)	118.1	(9)	O(1)	-C	(16)	-C	(15)	124.2	(6)
O(221)	-S	(22)	-C	(220)	110.8	(8)	C(11)	-C	(16)	-C	(15)	119.9	(6)
O(222)	-S	(22)	-C	(220)	109.2	(8)	S(21)	-C	(21)	-C	(22)	119.1	(7)
O(231)	-S	(23)	-O	(232)	119.4	(9)	S(21)	-C	(21)	-C	(26)	121.2	(7)
O(231)	-S	(23)	-C	(230)	108.9	(8)	C(22)	-C	(21)	-C	(26)	119.5	(7)
O(232)	-S	(23)	-C	(230)	107.9	(8)	C(21)	-C	(22)	-C	(23)	121.4	(7)
O(31)	-S	(3)	-O	(32)	116.3	(10)	C(22)	-C	(23)	-C	(24)	118.5	(7)
O(31)	-S	(3)	-C	(3)	109.5	(9)	O(4)	-C	(24)	-C	(23)	123.6	(7)
O(32)	-S	(3)	-C	(3)	109.9	(9)	O(4)	-C	(24)	-C	(25)	114.5	(6)
C(16)	-O	(1)	-Me	(1)	117.3	(5)	C(23)	-C	(24)	-C	(25)	121.9	(7)
C(14)	-O	(2)	-Me	(2)	118.5	(6)	C(24)	-C	(25)	-C	(26)	119.3	(7)
C(26)	-O	(3)	-Me	(3)	118.3	(6)	O(3)	-C	(26)	-C	(21)	115.6	(6)
C(24)	-O	(4)	-Me	(4)	118.4	(6)	O(3)	-C	(26)	-C	(25)	125.0	(6)
S(1)	-C	(11)	-C	(12)	117.6	(7)	C(21)	-C	(26)	-C	(25)	119.4	(7)

Table XXVII: Selected torsional angles for 55

O(11)	-S (1)	-C (11)	-C (12)	128 (1)
O(11)	-S (1)	-C (11)	-C (16)	-50 (1)
O(12)	-S (1)	-C (11)	-C (12)	-6 (1)
O(12)	-S (1)	-C (11)	-C (16)	177 (1)
O(211)	-S (21)	-C (21)	-C (22)	-128 (1)
O(211)	-S (21)	-C (21)	-C (26)	47 (1)
O(212)	-S (21)	-C (21)	-C (22)	5 (1)
O(212)	-S (21)	-C (21)	-C (26)	180 (1)
Me(1)	-O (1)	-C (16)	-C (11)	172 (1)
Me(1)	-O (1)	-C (16)	-C (15)	-10 (1)
Me(2)	-O (2)	-C (14)	-C (13)	-1 (1)
Me(2)	-O (2)	-C (14)	-C (15)	179 (1)
Me(3)	-O (3)	-C (26)	-C (21)	178 (1)
Me(3)	-O (3)	-C (26)	-C (25)	-1 (1)
Me(4)	-O (4)	-C (24)	-C (23)	4 (1)
Me(4)	-O (4)	-C (24)	-C (25)	-178 (1)
S(1)	-C (11)	-C (12)	-C (13)	-178 (1)
S(1)	-C (11)	-C (16)	-O (1)	-3 (1)
S(1)	-C (11)	-C (16)	-C (15)	178 (1)
C(16)	-C (11)	-C (12)	-C (13)	0 (1)
C(12)	-C (11)	-C (16)	-C (15)	1 (1)
C(11)	-C (12)	-C (13)	-C (14)	-1 (1)
C(12)	-C (13)	-C (14)	-O (2)	-177 (1)
C(12)	-C (13)	-C (14)	-C (15)	3 (1)
O(2)	-C (14)	-C (15)	-C (16)	177 (1)
C(13)	-C (14)	-C (15)	-C (16)	-3 (1)
C(14)	-C (15)	-C (16)	-O (1)	-178 (1)
C(14)	-C (15)	-C (16)	-C (11)	1 (1)
S(21)	-C (21)	-C (22)	-C (23)	172 (1)
S(21)	-C (21)	-C (26)	-O (3)	10 (1)
S(21)	-C (21)	-C (26)	-C (25)	-171 (1)
C(26)	-C (21)	-C (22)	-C (23)	-3 (1)
C(22)	-C (21)	-C (26)	-O (3)	-175 (1)
C(22)	-C (21)	-C (26)	-C (25)	3 (1)
C(21)	-C (22)	-C (23)	-C (24)	0 (1)
C(22)	-C (23)	-C (24)	-O (4)	-179 (1)
C(22)	-C (23)	-C (24)	-C (25)	3 (1)
O(4)	-C (24)	-C (25)	-C (26)	180 (1)
C(23)	-C (24)	-C (25)	-C (26)	-2 (1)
C(24)	-C (25)	-C (26)	-O (3)	177 (1)
C(24)	-C (25)	-C (26)	-C (21)	-1 (1)

Table XXVIII: Atomic parameters ($x10^4$, except $x\ 10^3$) for 55

Name	X/a	Y/b	Z/c	U_{iso}	Mod(U)
S(1)	2865 (13)	2213 (10)	811 (9)		389 (67)
S(2)	1986 (13)	3196 (11)	2415 (9)		413 (69)
S(21)	653 (13)	3179 (10)	-2495 (9)		384 (67)
S(22)	827 (13)	654 (10)	-1709 (8)		352 (64)
S(23)	835 (14)	1957 (10)	-3864 (8)		379 (66)
S(3)	3788 (14)	704 (10)	2857 (9)		401 (69)
O(1)	5944 (5)	2776 (4)	261 (3)	423 (12)	
O(11)	3894 (6)	1229 (4)	640 (4)	489 (13)	
O(12)	1199 (6)	2339 (4)	909 (4)	492 (13)	
O(2)	3961 (6)	6428 (4)	-2045 (3)	459 (12)	
O(21)	729 (6)	2698 (5)	2892 (4)	559 (14)	
O(211)	750 (6)	2900 (4)	-1490 (4)	489 (13)	
O(212)	-842 (6)	3733 (4)	2929 (4)	520 (13)	
O(22)	1668 (6)	4234 (4)	1604 (4)	510 (13)	
O(221)	-770 (6)	1073 (4)	-1412 (4)	494 (13)	
O(222)	1189 (6)	-282 (4)	-2045 (4)	490 (13)	
O(231)	-760 (6)	1880 (4)	-3770 (4)	514 (13)	
O(232)	1221 (6)	2962 (4)	-4534 (4)	486 (13)	
O(3)	4027 (6)	2560 (4)	-2176 (4)	503 (13)	
O(31)	5164 (6)	8 (4)	2545 (4)	534 (13)	
O(32)	3849 (6)	804 (5)	3760 (4)	583 (15)	
O(4)	4984 (6)	6029 (5)	-4374 (4)	590 (14)	
Hm(11)	809 (11)	226 (8)	43 (7)	90 (32)	
Hm(12)	769 (10)	355 (7)	-1 (6)	72 (27)	
Hm(13)	764 (7)	293 (5)	-65 (4)	32 (18)	
Hm(21)	219 (37)	666 (26)	-244 (22)	605 (111)	

Table XXVIII: (cont.)

Hm(22)	299 (26)	734 (18)	-294 (15)	433 (93)
Hm(23)	267 (26)	748 (18)	-219 (16)	482 (101)
Hm(31)	552 (9)	151 (7)	-151 (6)	66 (26)
Hm(32)	590 (8)	265 (6)	-164 (5)	52 (20)
Hm(33)	631 (7)	217 (5)	-264 (5)	43 (19)
Hm(41)	550 (11)	735 (8)	-522 (7)	102 (33)
Hm(42)	357 (9)	763 (7)	-482 (6)	72 (25)
Hm(43)	406 (9)	710 (7)	-566 (6)	67 (25)
H(1)	442 (10)	235 (7)	180 (6)	58 (27)
H(12)	94 (9)	410 (7)	-27 (6)	71 (25)
H(13)	68 (26)	528 (21)	-103 (17)	436 (108)
H(15)	623 (21)	441 (16)	-99 (13)	243 (87)
H(21)	318 (8)	281 (6)	367 (5)	56 (22)
H(210)	280 (33)	139 (25)	-284 (21)	541 (107)
H(220)	55 (8)	515 (6)	-409 (5)	66 (22)
H(22)	233 (12)	394 (9)	339 (7)	117 (37)
H(221)	205 (12)	92 (9)	-60 (7)	94 (35)
H(222)	314 (9)	6 (7)	-97 (6)	77 (26)
H(223)	181 (11)	-20 (8)	-39 (7)	95 (32)
H(23)	371 (12)	368 (9)	296 (7)	70 (35)
H(230)	209 (9)	635 (6)	-480 (5)	75 (24)
H(231)	179 (9)	17 (7)	-370 (6)	88 (26)
H(232)	178 (10)	93 (8)	-481 (7)	109 (31)
H(233)	304 (9)	79 (7)	-410 (6)	62 (26)
H(25)	563 (10)	408 (7)	-311 (6)	86 (28)

Table XXVIII: (cont.)

H(31)	206 (7)	19 (5)	231 (4)	31 (17)
H(32)	126 (13)	68 (9)	309 (8)	120 (39)
H(33)	224 (10)	-49 (8)	347 (6)	104 (30)
C(1)	3441 (8)	2142 (5)	1964 (5)	381 (16)
C(11)	3230 (7)	3452 (5)	-28 (5)	345 (15)
C(12)	1953 (7)	4296 (5)	-519 (5)	378 (15)
C(13)	2133 (8)	5296 (6)	-1217 (5)	405 (16)
C(14)	3648 (8)	5451 (5)	-1403 (5)	377 (16)
C(15)	4959 (7)	4626 (5)	-949 (5)	361 (15)
C(16)	4757 (7)	3629 (5)	-257 (5)	342 (15)
C(2)	2921 (9)	3390 (7)	3248 (5)	532 (19)
C(21)	1993 (8)	3966 (5)	-3126 (5)	372 (16)
C(210)	1425 (7)	1808 (5)	-2700 (5)	345 (15)
C(22)	1466 (8)	4989 (6)	-3855 (5)	453 (17)
C(220)	2117 (8)	335 (6)	-808 (5)	479 (18)
C(23)	2424 (8)	5705 (6)	-4300 (5)	474 (18)
C(230)	2082 (9)	784 (7)	-4130 (6)	563 (20)
C(24)	3937 (8)	5379 (6)	-3995 (5)	432 (17)
C(25)	4532 (8)	4338 (6)	-3288 (5)	421 (16)
C(26)	3570 (8)	3619 (6)	-2853 (5)	405 (16)
C(3)	2145 (9)	228 (7)	2854 (6)	596 (21)
Me(1)	7542 (8)	2857 (6)	-38 (5)	463 (17)
Me(2)	2653 (9)	7345 (7)	-2571 (6)	560 (20)
Me(3)	5644 (9)	2138 (7)	-1894 (5)	545 (20)
Me(4)	4460 (10)	7126 (7)	-5082 (6)	663 (23)

Table XXIX: Anisotropic temperature factors for 55

Name	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	345 (64)	394 (67)	430 (69)	-156 (55)	-34 (51)	-123 (53)
S(2)	282 (60)	461 (73)	496 (74)	-220 (60)	27 (51)	-81 (52)
S(21)	325 (63)	331 (65)	498 (73)	-146 (56)	10 (53)	-45 (51)
S(22)	360 (65)	340 (63)	355 (64)	-60 (51)	21 (50)	-102 (51)
S(23)	399 (67)	396 (68)	343 (63)	-60 (53)	-38 (51)	-153 (54)

APPENDIX III

X-RAY DATA FOR **141**

Figure XXV: X-ray structure for the unit cell of **141**

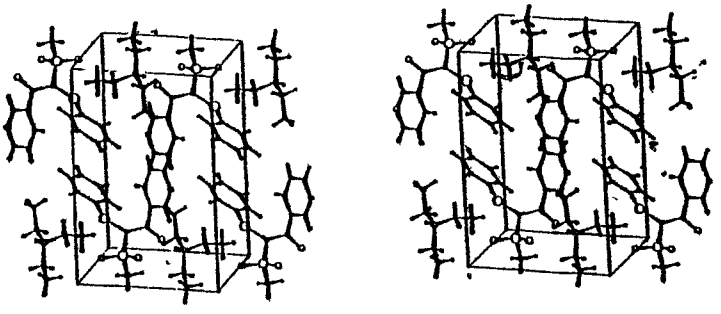

Table XXX: Interatomic bond distances for 141

C(1)	-N(1)	1.324 (4)	S(2)	-C(9)	1.770 (3)
C(1)	-C(5)	1.391 (2)	C(9)	-C(10)	1.389 (4)
N(1)	-C(2)	1.318 (4)	C(9)	-C(14)	1.373 (4)
C(2)	-C(3)	1.373 (5)	C(10)	-C(11)	1.370 (5)
C(3)	-C(4)	1.367 (4)	C(11)	-C(12)	1.349 (5)
C(4)	-C(5)	1.382 (3)	C(12)	-C(13)	1.376 (5)
C(5)	-C(6)	1.494 (3)	C(13)	-C(14)	1.383 (4)
C(6)	-O(1)	1.263 (3)	N(2)	-C(15)	1.491 (3)
C(6)	-C(7)	1.396 (4)	N(2)	-C(17)	1.490 (4)
C(7)	-S(1)	1.744 (3)	N(2)	-C(19)	1.510 (3)
C(7)	-S(2)	1.734 (3)	C(15)	-C(16)	1.490 (5)
S(1)	-O(2)	1.446 (2)	C(17)	-C(18)	1.489 (5)
S(1)	-O(3)	1.433 (2)	C(19)	-C(20)	1.498 (4)
S(1)	-C(8)	1.755 (3)			

Table XXXI: Interbond angles for **141**

N(1)	-C(1)	-C(5)	124.8 (3)	O(2)	-S(1)	-C(8)	107.4 (1)
C(1)	-N(1)	-C(2)	116.9 (3)	O(3)	-S(1)	-C(8)	107.7 (1)
N(1)	-C(2)	-C(3)	123.4 (3)	C(7)	-S(2)	-C(9)	106.8 (1)
C(2)	-C(3)	-C(4)	119.1 (3)	S(2)	-C(9)	-C(10)	116.4 (2)
C(3)	-C(4)	-C(5)	119.4 (3)	S(2)	-C(9)	-C(14)	124.6 (2)
C(1)	-C(5)	-C(4)	116.4 (2)	C(10)	-C(9)	-C(14)	119.0 (3)
C(1)	-C(5)	-C(6)	118.5 (2)	C(9)	-C(10)	-C(11)	120.2 (3)
C(4)	-C(5)	-C(6)	124.9 (2)	C(10)	-C(11)	-C(12)	121.0 (3)
C(5)	-C(6)	-O(1)	115.6 (2)	C(11)	-C(12)	-C(13)	119.5 (3)
C(5)	-C(6)	-C(7)	120.9 (2)	C(12)	-C(13)	-C(14)	120.6 (3)
O(1)	-C(6)	-C(7)	123.6 (2)	C(9)	-C(14)	-C(13)	119.7 (3)
C(6)	-C(7)	-S(1)	117.7 (2)	C(15)	-N(2)	-C(17)	110.7 (2)
C(6)	-C(7)	-S(2)	124.3 (2)	C(15)	-N(2)	-C(19)	113.1 (2)
S(1)	-C(7)	-S(2)	116.8 (1)	C(17)	-N(2)	-C(19)	113.0 (2)
C(7)	-S(1)	-O(2)	109.2 (1)	N(2)	-C(15)	-C(16)	113.0 (2)
C(7)	-S(1)	-O(3)	110.0 (1)	N(2)	-C(17)	-C(18)	113.3 (3)
C(7)	-S(1)	-C(8)	106.2 (1)	N(2)	-C(19)	-C(20)	113.3 (2)
O(2)	-S(1)	-O(3)	115.9 (1)				

Table XXXII: Selected torsional angles for **141**

C(5)	-C (1)	-N (1)	-C (2)	1.1 (5)
N(1)	-C (1)	-C (5)	-C (4)	-.8 (4)
N(1)	-C (1)	-C (5)	-C (6)	-176.0 (3)
C(1)	-N (1)	-C (2)	-C (3)	-.6 (5)
N(1)	-C (2)	-C (3)	-C (4)	-.1 (5)
C(2)	-C (3)	-C (4)	-C (5)	.5 (5)
C(3)	-C (4)	-C (5)	-C (1)	-.0 (4)
C(3)	-C (4)	-C (5)	-C (6)	174.9 (3)
C(1)	-C (5)	-C (6)	-O (1)	37.9 (4)
C(1)	-C (5)	-C (6)	-C (7)	-141.1 (3)
C(4)	-C (5)	-C (6)	-O (1)	-136.9 (3)
C(4)	-C (5)	-C (6)	-C (7)	44.1 (4)
C(5)	-C (6)	-C (7)	-S (1)	-178.3 (2)
C(5)	-C (6)	-C (7)	-S (2)	15.1 (3)
O(1)	-C (6)	-C (7)	-S (1)	2.7 (3)
O(1)	-C (6)	-C (7)	-S (2)	-163.8 (2)
C(6)	-C (7)	-S (1)	-O (2)	178.9 (2)
C(6)	-C (7)	-S (1)	-O (3)	50.6 (3)
C(6)	-C (7)	-S (1)	-C (8)	-65.5 (3)
S(2)	-C (7)	-S (1)	-O (2)	-13.5 (2)
S(2)	-C (7)	-S (1)	-O (3)	-141.8 (2)
S(2)	-C (7)	-S (1)	-C (8)	102.0 (2)
S(1)	-C (7)	-S (2)	-C (9)	87.1 (2)
C(7)	-S (2)	-C (9)	-C (10)	-175.5 (2)
C(7)	-S (2)	-C (9)	-C (14)	5.5 (3)
S(2)	-C (9)	-C (10)	-C (11)	-177.9 (2)
S(2)	-C (9)	-C (14)	-C (13)	178.3 (2)
C(14)	-C (9)	-C (10)	-C (11)	1.1 (4)
C(10)	-C (9)	-C (14)	-C (13)	-.7 (4)
C(9)	-C (10)	-C (11)	-C (12)	-.9 (5)
C(10)	-C (11)	-C (12)	-C (13)	0 (1)
C(11)	-C (12)	-C (13)	-C (14)	0 (1)
C(12)	-C (13)	-C (14)	-C (9)	0 (1)
C(17)	-N (2)	-C (15)	-C (16)	-170.8 (3)
C(15)	-N (2)	-C (17)	-C (18)	170.4 (3)
C(19)	-N (2)	-C (15)	-C (16)	61.1 (3)
C(15)	-N (2)	-C (19)	-C (20)	58.4 (3)
C(19)	-N (2)	-C (17)	-C (18)	-61.5 (3)
C(17)	-N (2)	-C (19)	-C (20)	-68.4 (3)

Table XXXIII: Atomic parameters (x10^4, except x 10^3 for hydrogen and 10^5 for S(1)) for **141**

Name	X/a	Y/b	Z/c	U_{iso}	Mod(U)
C(1)	3012 (3)	4834 (3)	2576 (2)		503 (15)
N(1)	2023 (3)	5106 (3)	3208 (2)		638 (15)
C(2)	2073 (4)	4646 (3)	4059 (2)		575 (17)
C(3)	3073 (4)	3904 (4)	4306 (2)		589 (17)
C(4)	4073 (3)	3614 (3)	3642 (2)		516 (15)
C(5)	4066 (3)	4083 (3)	2742 (2)		365 (12)
C(6)	5188 (3)	3959 (3)	1981 (2)		351 (12)
O(1)	5785 (2)	5159 (2)	1549 (1)		445 (10)
C(7)	5509 (3)	2582 (3)	1768 (2)		396 (13)
S(1)	68758 (7)	25652 (7)	8911 (4)		3977 (35)
O(2)	7067 (2)	1058 (2)	790 (1)		563 (11)
O(3)	8354 (2)	3969 (2)	1101 (1)		526 (11)
C(8)	5943 (4)	2657 (3)	-205 (2)		545 (16)
S(2)	4360 (1)	764 (1)	2128 (0)		406 (4)
C(9)	5544 (3)	508 (3)	3075 (2)		412 (13)
C(10)	4898 (3)	-938 (3)	3427 (2)		519 (16)
C(11)	5710 (4)	-1215 (4)	4180 (2)		663 (19)
C(12)	7156 (4)	-107 (4)	4584 (2)		692 (20)
C(13)	7820 (4)	1325 (4)	4237 (2)		592 (17)
C(14)	7017 (3)	1636 (3)	3482 (2)		473 (15)
N(2)	8918 (2)	-2541 (2)	1684 (1)		368 (10)
C(15)	9961 (3)	-2791 (3)	2442 (2)		467 (14)
C(16)	9140 (4)	-3133 (4)	3354 (2)		701 (20)
C(17)	9682 (3)	-2466 (3)	741 (2)		480 (15)
C(18)	8581 (5)	-2489 (5)	-82 (2)		730 (22)
C(19)	8451 (3)	-1140 (3)	1991 (2)		473 (14)
C(20)	9896 (4)	409 (3)	2254 (3)		632 (18)

Table XXXIII: (cont.)

H(1)	298 (3)	515 (4)	194 (2)	53 (8)
H(2)	133 (4)	487 (4)	452 (2)	62 (8)
H(3)	312 (4)	371 (4)	490 (2)	60 (8)
H(4)	481 (4)	319 (4)	381 (2)	65 (9)
H(81)	679 (5)	280 (5)	-64 (3)	102 (14)
H(82)	507 (4)	173 (4)	-36 (2)	69 (9)
H(83)	565 (4)	357 (4)	-8 (3)	77 (10)
H(10)	391 (4)	-168 (4)	312 (2)	56 (8)
H(11)	525 (5)	-207 (5)	444 (3)	100 (13)
H(12)	768 (4)	-27 (4)	506 (3)	79 (11)
H(13)	881 (4)	202 (4)	450 (2)	64 (9)
H(14)	752 (3)	260 (4)	320 (2)	53 (8)
HN(2)	808 (3)	-332 (3)	160 (2)	35 (6)
H(151)	1095 (3)	-190 (3)	253 (2)	42 (7)
H(152)	1020 (4)	-371 (4)	215 (2)	64 (9)
H(161)	805 (6)	-392 (6)	330 (4)	105 (16)
H(162)	980 (5)	-346 (5)	375 (3)	98 (13)
H(163)	902 (5)	-234 (5)	370 (3)	90 (12)
H(171)	1070 (3)	-162 (3)	84 (2)	36 (6)
H(172)	993 (4)	-335 (4)	63 (2)	58 (8)
H(181)	751 (5)	-322 (5)	-6 (3)	92 (12)
H(182)	909 (4)	-262 (4)	-67 (2)	70 (10)
H(183)	831 (5)	-159 (6)	1 (3)	101 (14)
H(191)	782 (3)	-136 (3)	253 (2)	41 (7)
H(192)	778 (4)	-112 (4)	148 (2)	67 (9)
H(201)	1045 (5)	50 (5)	294 (3)	86 (11)
H(202)	1071 (4)	56 (4)	175 (3)	73 (10)
H(203)	954 (4)	111 (4)	228 (3)	79 (11)

Table XXXIV: Anisotropic temperature factors for **141**

Name	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	599 (16)	378 (14)	533 (15)	134 (12)	58 (13)	344 (13)
N(1)	651 (15)	550 (15)	712 (16)	162 (13)	148 (13)	456 (13)
C(2)	633 (18)	424 (16)	670 (19)	138 (14)	223 (14)	325 (14)
C(3)	766 (20)	500 (17)	502 (16)	211 (13)	192 (14)	384 (15)
C(4)	599 (16)	426 (15)	523 (16)	176 (12)	105 (13)	362 (13)
C(5)	413 (13)	202 (11)	480 (14)	81 (10)	26 (10)	176 (10)
C(6)	358 (12)	266 (13)	429 (13)	109 (10)	7 (10)	162 (9)
O(1)	461 (9)	293 (9)	582 (10)	191 (8)	100 (8)	207 (8)
C(7)	443 (13)	266 (13)	480 (14)	133 (10)	72 (11)	217 (11)
S(1)	4481 (35)	2704 (33)	4747 (37)	1053 (26)	778 (27)	2311 (27)
O(2)	645 (12)	367 (10)	677 (12)	163 (9)	154 (9)	388 (9)
O(3)	449 (10)	438 (11)	691 (12)	71 (9)	121 (9)	179 (8)
C(8)	685 (18)	458 (16)	491 (15)	102 (12)	45 (13)	333 (14)
S(2)	422 (3)	245 (3)	550 (4)	127 (3)	47 (3)	159 (3)
C(9)	482 (13)	272 (13)	481 (13)	110 (10)	117 (11)	263 (11)
C(10)	543 (16)	334 (14)	681 (18)	208 (13)	136 (13)	244 (12)
C(11)	754 (20)	506 (18)	728 (19)	343 (16)	190 (16)	413 (16)
C(12)	851 (23)	658 (21)	566 (17)	240 (15)	73 (16)	528 (19)
C(13)	637 (17)	517 (18)	623 (18)	36 (14)	-77 (14)	323 (14)
C(14)	538 (15)	306 (13)	574 (16)	102 (11)	45 (12)	233 (12)
N(2)	355 (10)	269 (10)	482 (11)	111 (9)	41 (8)	160 (8)
C(15)	465 (14)	390 (14)	548 (15)	101 (12)	-12 (11)	272 (11)
C(16)	846 (22)	740 (22)	519 (16)	193 (15)	34 (15)	496 (18)
C(17)	531 (15)	361 (14)	549 (15)	131 (12)	171 (12)	222 (12)
C(18)	832 (23)	847 (25)	513 (17)	247 (16)	135 (16)	367 (20)
C(19)	460 (13)	386 (14)	575 (15)	160 (12)	98 (11)	307 (12)

APPENDIX IV

CALCULATION OF CARBON-13 CHEMICAL SHIFTS

Calculation of carbon-13 chemical shifts.

In Part III of this thesis a correlation of sulphur-33 chemical shift versus carbon-13 chemical shift data was presented for a series of sulphones and their corresponding hydrocarbons where the sulphone moiety is replaced by a methylene group. Unfortunately not all of the chemical shifts required for the hydrocarbons are known. Thus, those that were not available in the literature were calculated.

In 1964 calculations based on a broad range of hydrocarbons enabled Grant and Paul[278] to derive an estimate of carbon-13 resonance position which agreed fairly closely with the experimentally determined value. These calculations were much improved by Lindeman and Adams[264] after several technological developments enabled carbon-13 chemical shifts to be determined more accurately. The calculation method due to Lindeman and Adams is the one used here. Calculations of a chemical shift is simply a matter of putting numbers into a formula. For substituted hydrocarbons a less accurate, but still useful calculation of chemical shift can be made using the substituent effects upon replacement of a hydrogen atom with the substituent as shown in Table XXXV. In all cases shown in the table the numbers should be added to the chemical shift of the parent hydrocarbon. The parent hydrocarbons required in order

to do the calculations along with the chemical shift of the carbon atom of interest are listed in Table XXXVI. The data shown in these two tables were used to obtain the carbon-13 chemical shifts for the fourteen compounds shown in Table XVIII, (page 199). One such example is given below.

For $PhCOCH(Cl)\underline{C}H_2CH_3$ (entry #27 in Table XVIII).

Parent hydrocarbon:	15.34
Cl atom XX to C:	+11.0
PhCO group XX to C:	+ 1.0
Chemical shift =	27.34

Comments

For entry #20, $EtSO_2CH_2SO_2Et$ the parent hydrocarbon used was $EtCH_2CH_3$ and the effect of one SO_2Et moiety on the other was assumed to be the same as the effect of a -COR group.

The data presented here has assumed the same effect for the -COMe and a -COPh groups since only one parameter was available as shown in Table XXXV.

The calculation for the ketal assumed two α-OR groups.

For singly substituted compounds these type of calculations are probably reasonable but for multisubstitution the errors are magnified. Although the data obtained is by no means quantitative the linear

correlations obtained in Part III of the thesis justify the results. Obviously experimentally determined values are preferable.

Table XXXV: Data for calculation of chemical shifts.[279]

Substituent:	Effect:		
	α	β(st)*	β(br)*
COR	-	1	-
Ph	23	9	-
Cl	-	11	10
Br	-	11	10
SR	-	7	-
OR	-	8	5

*st = straight chain ; br = branded chain.

Table XXXVI: Carbon-13 chemical shifts for the parent hydrocarbons required for calculations.

Hydrocarbon:	Chemical shift:
$CH_3\underline{C}H_3$	6.80
$\underline{C}H_3CH_2\underline{C}H_3$	16.36
$\underline{C}H_3\underline{C}H_2\underline{C}H_3$	15.34
$CH_3\underline{C}H_2\underline{C}H_2\underline{C}H_3$	25.09

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