NEW ROUTES TO PHENOLS AND RELATED COMPOUNDS

A thesis presented by

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In partial fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY

OF

THE CITY UNIVERSITY

The City University

London

December 1979

CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Peter Sammes, for the opportunity of working in his Department and for his boundless, infectious enthusiasm in all chemical matters.

I gratefully acknowledge the financial support of Roussel Laboratories Ltd., and particularly the interest shown in this work by [redacted] I also thank the technical staff at the City University and [redacted] for patient and efficient typing.

My warmest thanks to all of my colleagues, especially [redacted] for creating a stimulating and good-humoured environment.

Finally, and most of all, I would like to thank my kith and kin for their loving support and encouragement during the course of this work.

To my parents

ABSTRACT

The mechanism and scope of the Pummerer reaction is reviewed.

Attempts to prepare the biogenetic precursors of resorcinols from dehydroacetic acid are described.

A convenient preparation of a γ,δ-unsaturated acetoacetate has been developed, and attempts to induce its aromatisation are discussed.

A novel one-step synthesis of 5-substituted resorcinols has been achieved by condensing methyl (phenylsulphinyl)-acetate (MPSA) with α,β-unsaturated methyl ketones. The isolation of the intermediate cyclohexanediones has been accomplished and their structures are discussed. In the case of olivetol, these compounds were converted to their enol ethers and the relative stereochemistries of the four products were deduced.

An analogous route to 3,5-disubstituted and 2,3,5-trisubstituted phenols is described. The scope of these reactions is investigated.

Some transformations of products derived from the alkylation of phenylsulphinylacetone (PSA) dianion are discussed. An unusual Pummerer rearrangement of MPSA and PSA has been observed.

A simple synthesis of an α,β-unsaturated, α-phenylsulphinyl ester has been discovered. The potential of this type of compound as a synthetic intermediate is discussed and illustrated with examples.

REVIEW

"One picture is worth a thousand words"

(Chinese)

Introduction

The advent of dimethyl sulphoxide (its spectacular solvent properties, reactions of the anion, Pfitzner-Moffatt oxidations etc.) has undoubtedly helped to highlight the, remarkably versatile, chemistry of the sulphinyl group. The reactions of DMSO were thoroughly reviewed by Durst[1] in 1969, and the interest, in sulphoxides generally, has continued unabated. A transformation known as the Pummerer rearrangement is the subject of this survey.

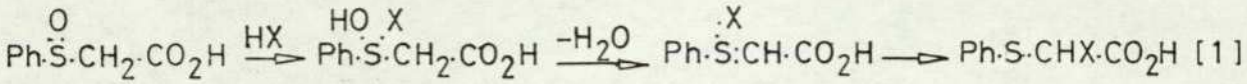
Historical

In 1909 Rudolf Pummerer[2] discovered that treatment of phenylsulphinylacetic acid with mineral acids gave thiophenol and glyoxylic acid. The same compound, with dry hydrogen chloride, yielded α-chlorophenylthioacetic acid. At the same time Smythe[3] noted that acidic reagents cleaved dibenzyl sulphoxide to unexpected products such as benzaldehyde, dibenzyl sulphide and the benzylthioacetal of benzaldehyde. He attempted to rationalise these observations by suggesting that the sulphoxide may exist as a mixture of keto- and enol-type tautomers, although recognising that "this type

$$PhCH_2SOCH_2Ph \rightleftharpoons PhCH_2SCHOHPh$$

of tautomerism is peculiar in that change from one form to another involves the transposition of the oxygen atom in the molecule". Pummerer postulated an alternative mechanism - subsequently shown to be correct, hence the name - which accounted for both the cleavage to thiophenol and glyoxylic

acid and the formation of the chlorosulphide under different conditions (Eqn. 1).

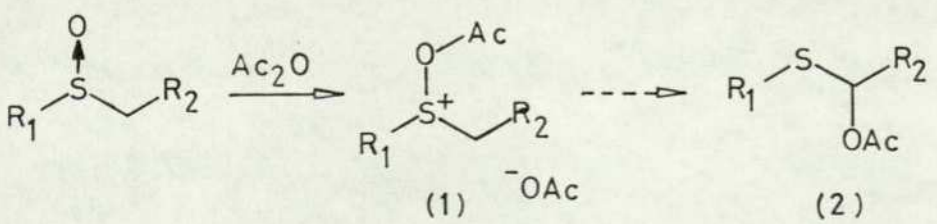


Half a century later Horner and Kaiser revived an interest in this unusual rearrangement by reporting that, on heating in acetic anhydride, sulphoxides with α-hydrogens gave good yields of α-acetoxy sulphides, or products derived from the latter.[4] This, coupled with the concurrent discovery of the oxidising properties of DMSO, and particularly the formation of methyl thiomethyl ethers as by-products, prompted a lively mechanistic debate.

Mechanism

It has been suggested[5] that the term "Pummerer rearrangement" should embrace all processes which involve the reduction of a sulphonium species with concomitant oxidation of the α-carbon. In this section emphasis will be placed on the reaction which has received most attention, i.e. the formation of α-acetoxysulphides from sulphoxides.

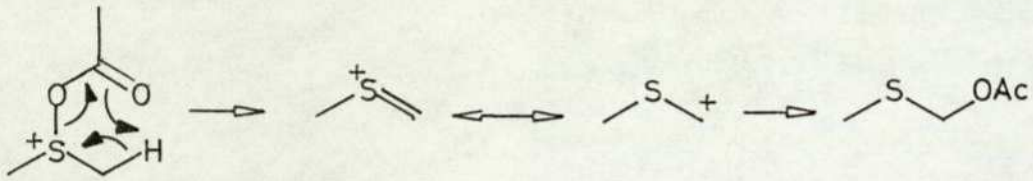
It is generally accepted that the first step, in the reaction of sulphoxides with acetic anhydride, is the formation of an acetoxysulphonium salt (1). On the other hand, the following stages leading to the products (2) have



been the subject of much speculation and considerable experimental effort. The majority of mechanisms which have been suggested for the Pummerer rearrangement can be divided into three classes, as summarised by Johnson and Phillips.[5] These are illustrated using the dimethylacetoxysulphonium salt.

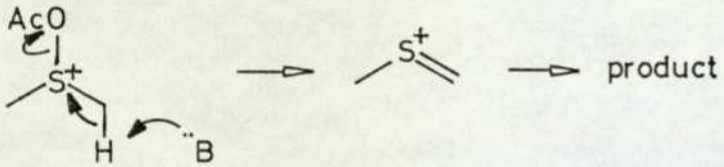
Carbonium Ion Intermediate

Concerted cyclic elimination of HOAc



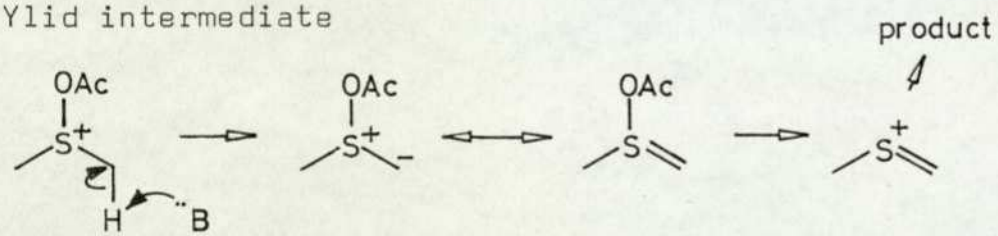
[2]

Concerted elimination of HOAc with external base



[3]

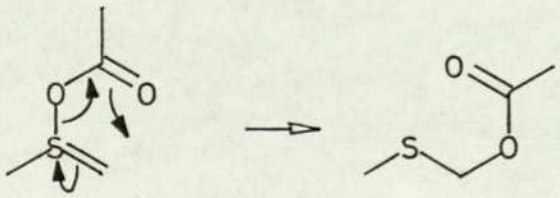
Ylid intermediate



[4]

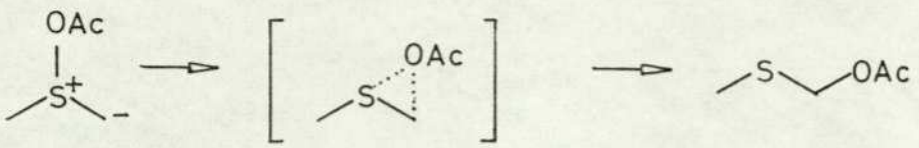
Internal Transfer of Acetoxy Group

Cyclic rearrangement



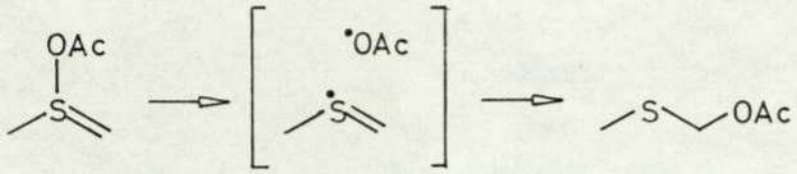
[5]

1,2-shift



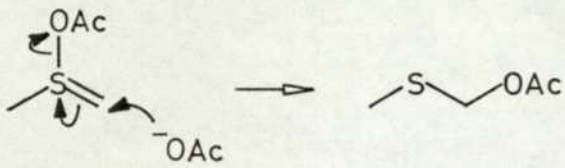
[6]

Homolytic dissociation-recombination



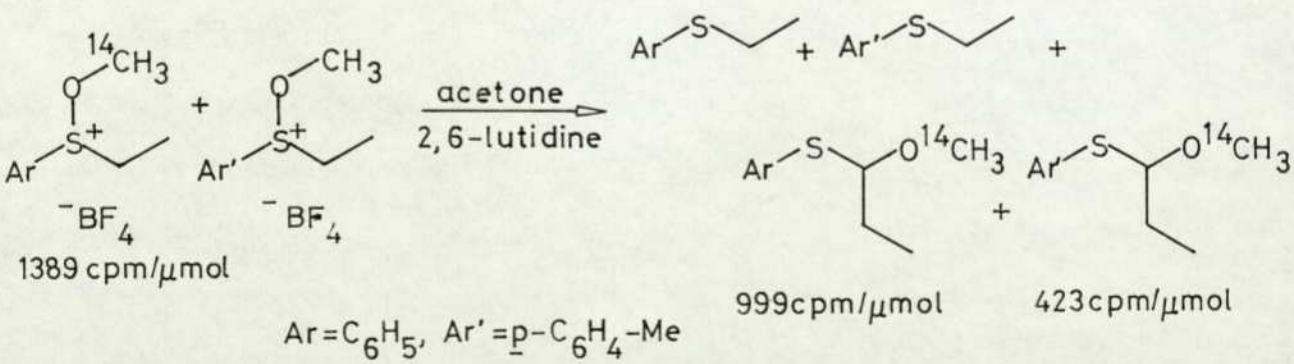
[7]

Nucleophilic Displacement of Ylid



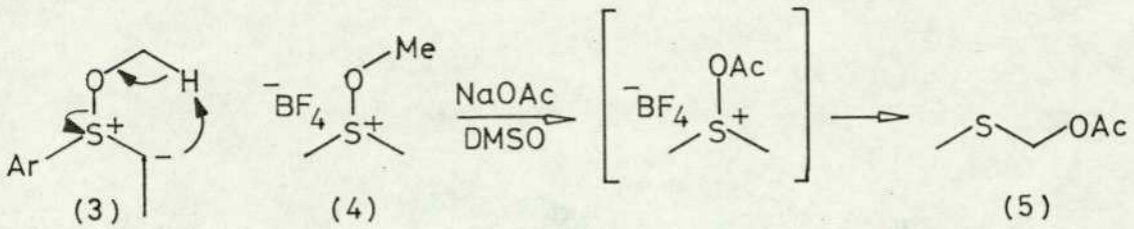
[8]

Following from their study of alkoxysulphonium salts,[6] the American authors used them as analogs of the acetoxysulphonium salts (1) to probe into the mechanism of the Pummerer reaction.[5] In an elegant crossover experiment they have shown that the alkoxy group escapes into solution,



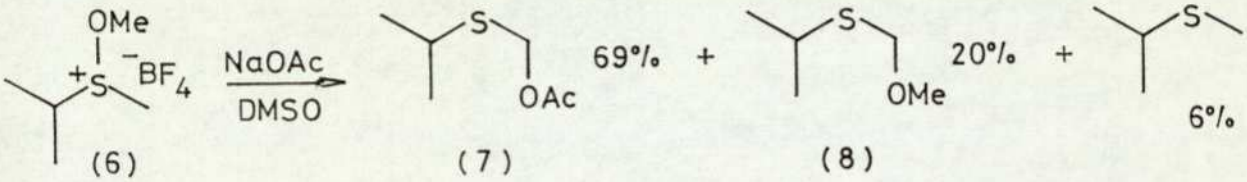
Ar=C_6H_5, Ar'=p-C_6H_4-Me

although the distribution of the label indicated a certain amount of ion-pair return. The formation of phenyl ethyl sulphide and p-tolyl ethyl sulphide is the result of the alternative mode of collapse of the ylid (3) to give formaldehyde (Moffatt-type oxidation). Further, the



(3) (4) (5)

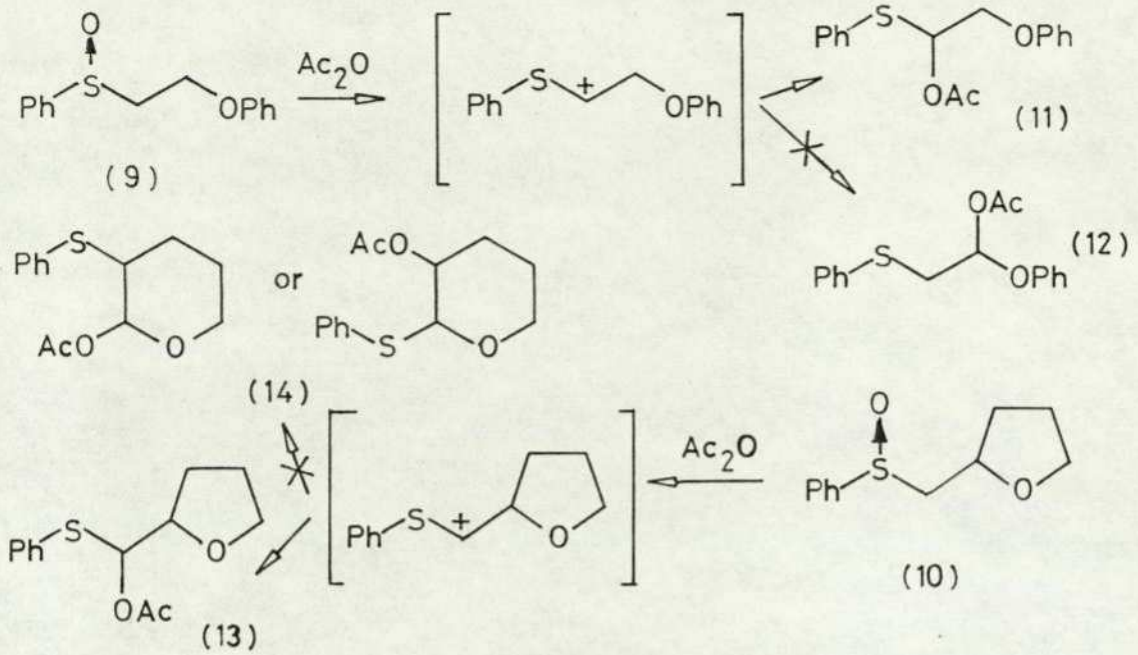
similarity to the acetoxysulphonium salts was established, since dimethylmethoxysulphonium fluoroborate (4) gave the α-acetoxy sulphide (5). Finally, the unsymmetric salt (6), on treatment with sodium acetate, collapsed to the products



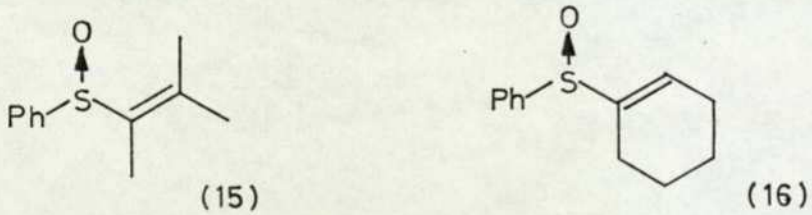
(6) (7) (8)

(7) and (8). Similar examples established that the migration occurred to the least substituted carbon. Taken together, these results pointed to the ylid intermediate mechanism (Eqn. 4). In other words proton removal to form the ylid was considered to be the rate- and product-determining step. A similar conclusion has been reached by Oae and co-workers.[7] However, the mechanism proposed by the Japanese workers, i.e. nucleophilic displacement of the ylid (Eqn. 8) moved Johnson to comment:- "The carbanionic site of an ylid appears to the present authors as a highly unlikely centre for nucleophilic attack. The suggestion that this type of reaction occurs appears to be without precedent elsewhere in the literature."[5]

Parham and Edwards[8] have sought to establish the intermediacy of a carbonium ion by investigating the Pummerer reaction of β-(phenylsulphinyl)phenetole (9) and of the tetrahydrofurfuryl sulphoxide (10). Both compounds were



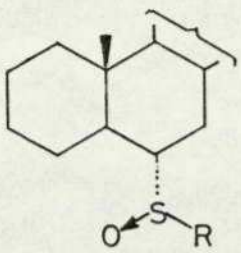
expected to give some rearranged products (12) and (14). Treatment with hot acetic anhydride, however, yielded only the normal Pummerer products (11) and (13). It was concluded that the sulphur-stabilised carbonium ions, if formed, were rapidly solvolysed. The stability of the vinyl sulphoxides (15) and (16), under similar conditions, was



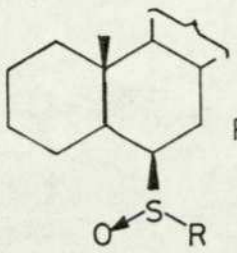
taken as evidence that the elimination of acetic acid from the acetoxysulphonium salt (1) proceeded via the cyclic elimination mechanism (Eqn. 2). With unsymmetric sulphoxides, the migration to the least substituted carbon was again predominant although not exclusive.

In a characteristically thorough study, Jones and co-workers[9] have provided compelling evidence of the effects of steric compression on the course of the Pummerer

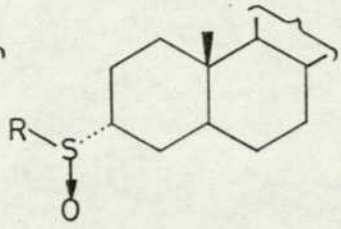
rearrangement. The reactions of the steroidal derivatives (17), (18), (19) and (20) with acetic anhydride were examined. Generally, it was found that products resulting



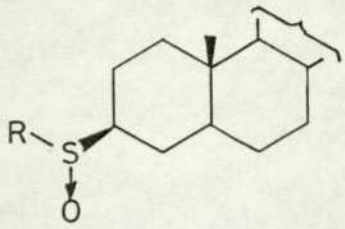
(17)



(18)

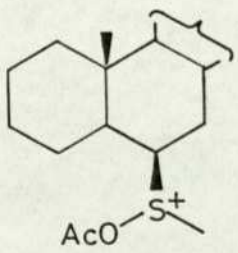


(19)



(20)

from the abstraction of the most acidic proton were formed, except in the 6β- (18) and, to a lesser degree, in the 3α- (19) series. In the 6β- case only the products resulting from the migration to the more highly substituted carbon (i.e. the ring position) were observed. This apparent anomaly was rationalised by assuming that the configuration at C(6) in the intermediate ylid (22) was roughly planar and that the transition state connecting the salt (21) to the ylid has a great deal of ylid character.



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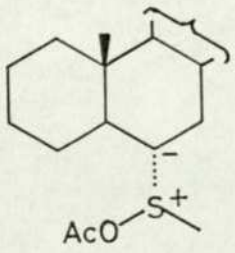
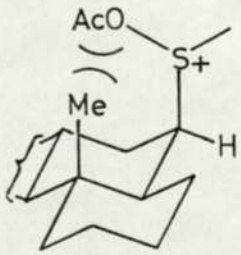
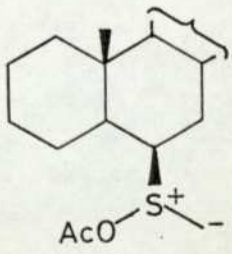


(22)



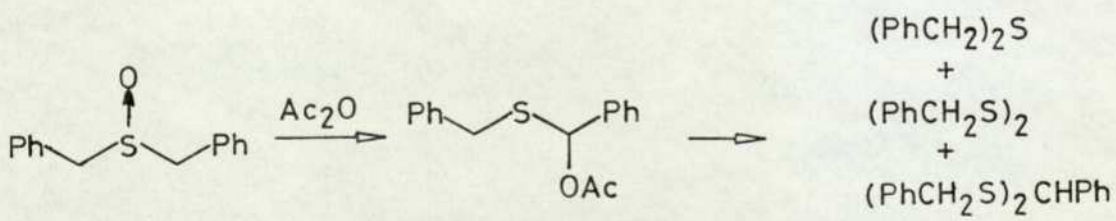


(23)

Conversion of (21) into (22) would be accompanied by the relief of steric interactions. No similar advantage is gained if the alternative ylid (23) were to form. Consequently the transition state leading to (22) could be energetically favoured over that leading to (23). In agreement with this

theory, in the 3α- case, where the steric congestion is less pronounced, migration in both directions was observed. Using the same arguments Jones has shown that the elimination of acetic acid, from the initially formed salt (21), is unlikely to proceed via the concerted, cyclic mechanism since the required transition state would cause an increase rather than decrease in steric crowding. He concluded, therefore, that the acetoxysulphonium salt (21) collapses to the sulphur stabilised carbonium ion either via the ylid intermediate (Eqn. 4), or that concerted elimination of acetic acid (Eqn. 3) proceeds through a transition state possessing appreciable ylid character.

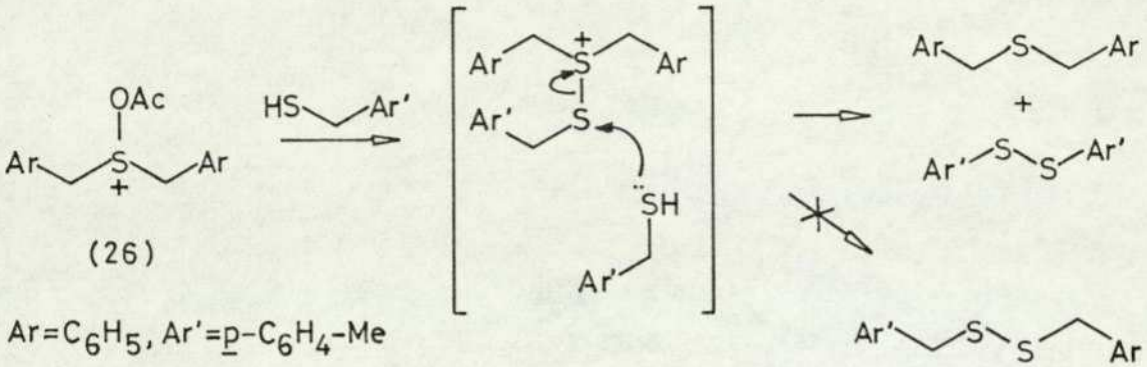
Wilson and Strong have re-examined in detail the reaction of dibenzyl sulphoxide with acetic anhydride.[10] The initially formed product was the expected α-acetoxybenzyl benzyl sulphide (24). As the reaction progressed dibenzyl-thioacetal of benzaldehyde (25), dibenzyl sulphide and dibenzyl disulphide would appear. The major product was (25).



(24) (25)

The minor components viz. the sulphide and the disulphide formed in approximately equal amounts. These secondary products were shown to be the result of an acid-catalysed disproportionation of (24). The sulphide was considered to arise from the attack of benzyl mercaptan on the acetoxy-

sulphonium salt (26), since addition of the thiol gave the sulphide and the disulphide as the only products. The disulphide was shown to originate from the added mercaptan

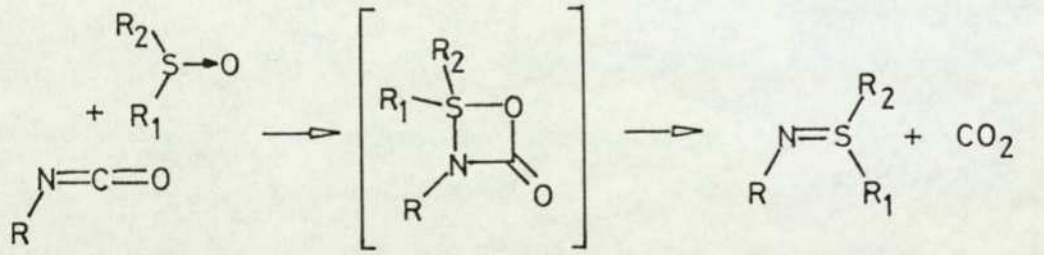


(26)

Ar=C_6H_5, Ar'=p-C_6H_4-Me

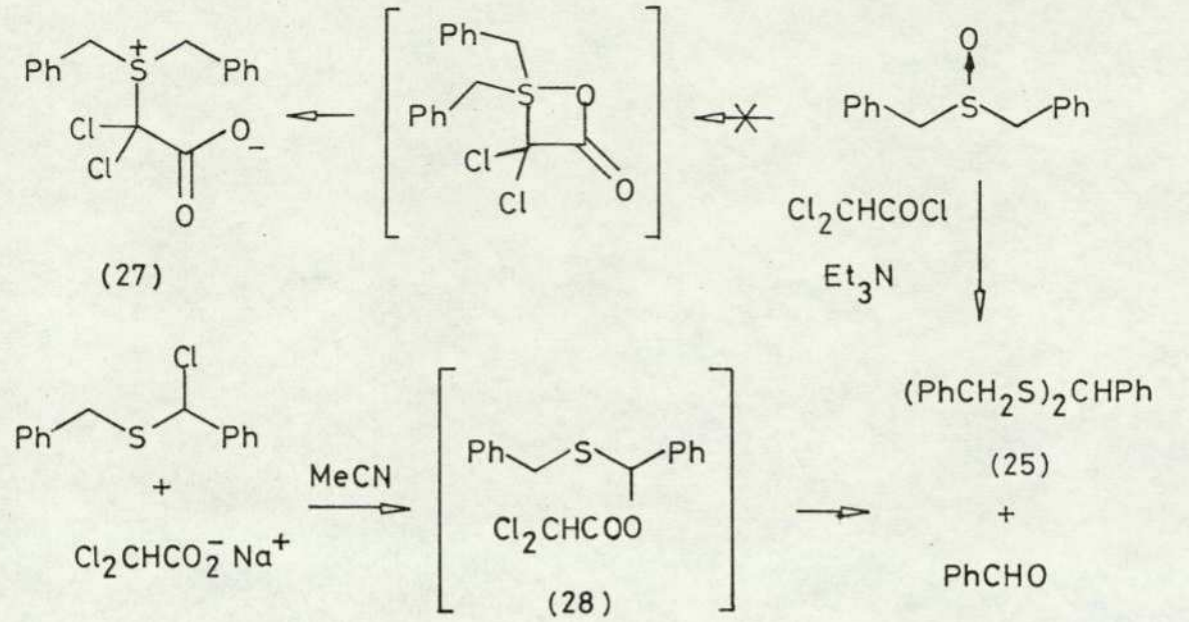
in a crossover experiment. Significantly, addition of pyridine completely suppressed this, and the disproportionation, reaction. The initial reaction exhibited a competitive isotope effect and this led to the conclusion that the elimination of acetic acid, in the absence of a strong base, was concerted (cf. Eqn. 3).

A similar disproportionation reaction of an α-acyloxy sulphide has been observed by Harris and Boekelheide.[11] In an attempt to extend the reaction of sulphoxides with isocyanates (Eqn. 9) to ketenes, they treated dibenzyl sulph-

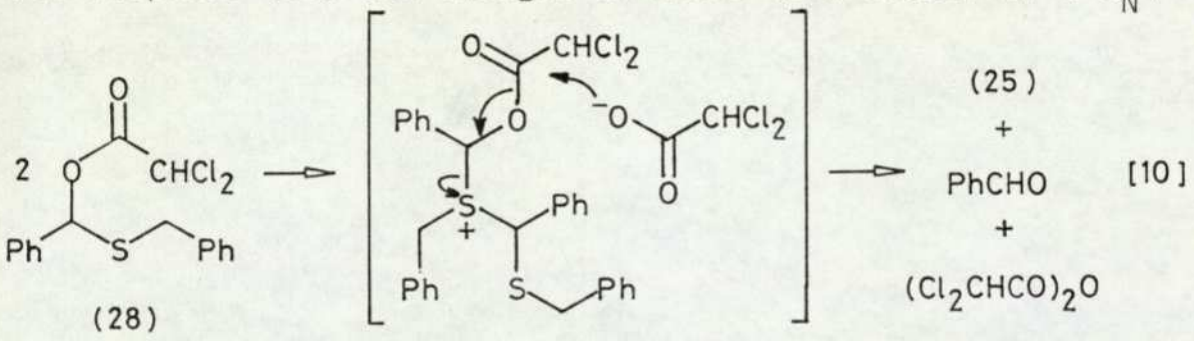


[9]

oxide with dichloroacetyl chloride in the presence of triethylamine. Instead of the desired product (27) a high yield of benzaldehyde and the dibenzylthioacetal (25) was obtained. These were shown to arise from the unstable α-dichloroacetoxybenzyl benzyl sulphide (28) because an

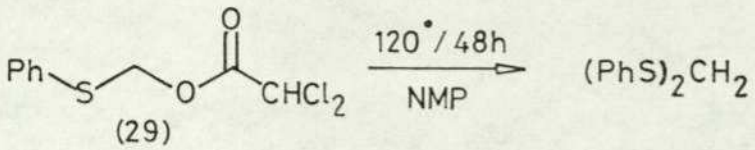


attempted synthesis of the latter gave the thioacetal (25). The sulphide (28) was thought to react with itself in a S_N1



or S_N2 process (Eqn. 10). It may be noted that the disproportionation of (28) occurred in non-acidic ambience, i.e. conditions under which acetoxybenzyl benzyl sulphide (24) was relatively stable.[10] However, the enhanced leaving ability of the dichloroacetate, as opposed to the acetate ion, could overcome that handicap leading to the sulphur-stabilised benzylic carbonium ion and hence to the products. Although Boekelheide did not explicitly invoke a carbonium ion, he found that methyl phenyl sulphoxide, which lacks benzylic activation, furnished only trace amounts of the diphenylthioacetal of benzaldehyde. However, thermolysis of the normal Pummerer product (29) in N-methyl pyrrolidone

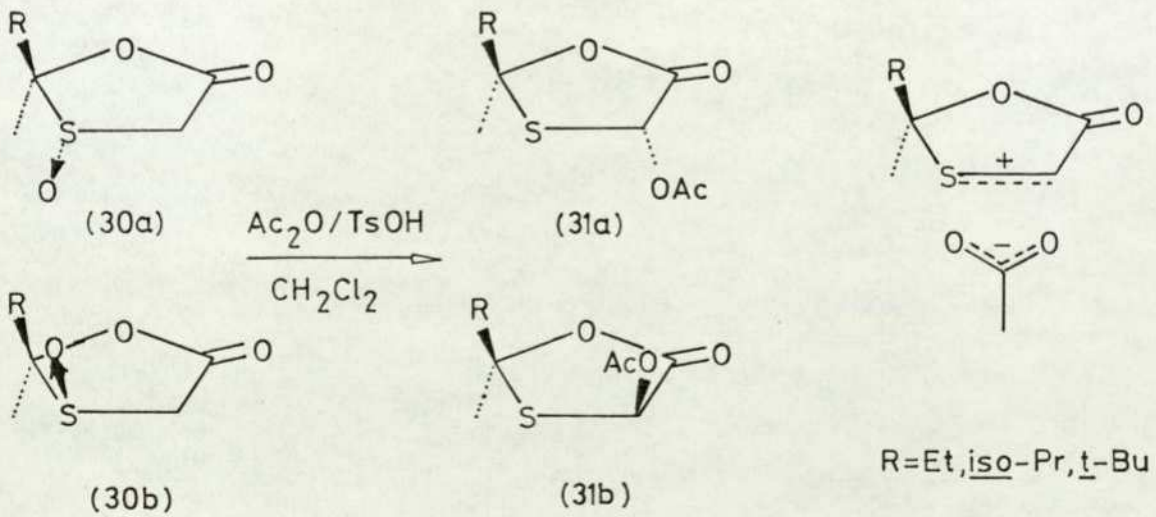
gave the thioacetal in 45% yield.



(29)

From the examples given thus far the following tentative guidelines can be drawn. First, the concerted elimination of acetic acid (Eqn. 3) seems to be the process favoured in neutral and acidic media. Secondly, the ylid intermediate (Eqn. 4) is probably formed in the presence of a base. Finally, the presumed, sulphur stabilised carbonium ion appears to be short-lived, except where additional stabilisation (e.g. benzyl) is available.

The first report of a stereospecific Pummerer rearrangement appeared in 1970.[12] The diastereoisomeric sulphoxides (30a) and (30b), on treatment with acetic anhydride gave the acetoxy sulphides (31a) and (31b) with 85-90% stereoselectivity. The appearance of the acetoxy group on the same



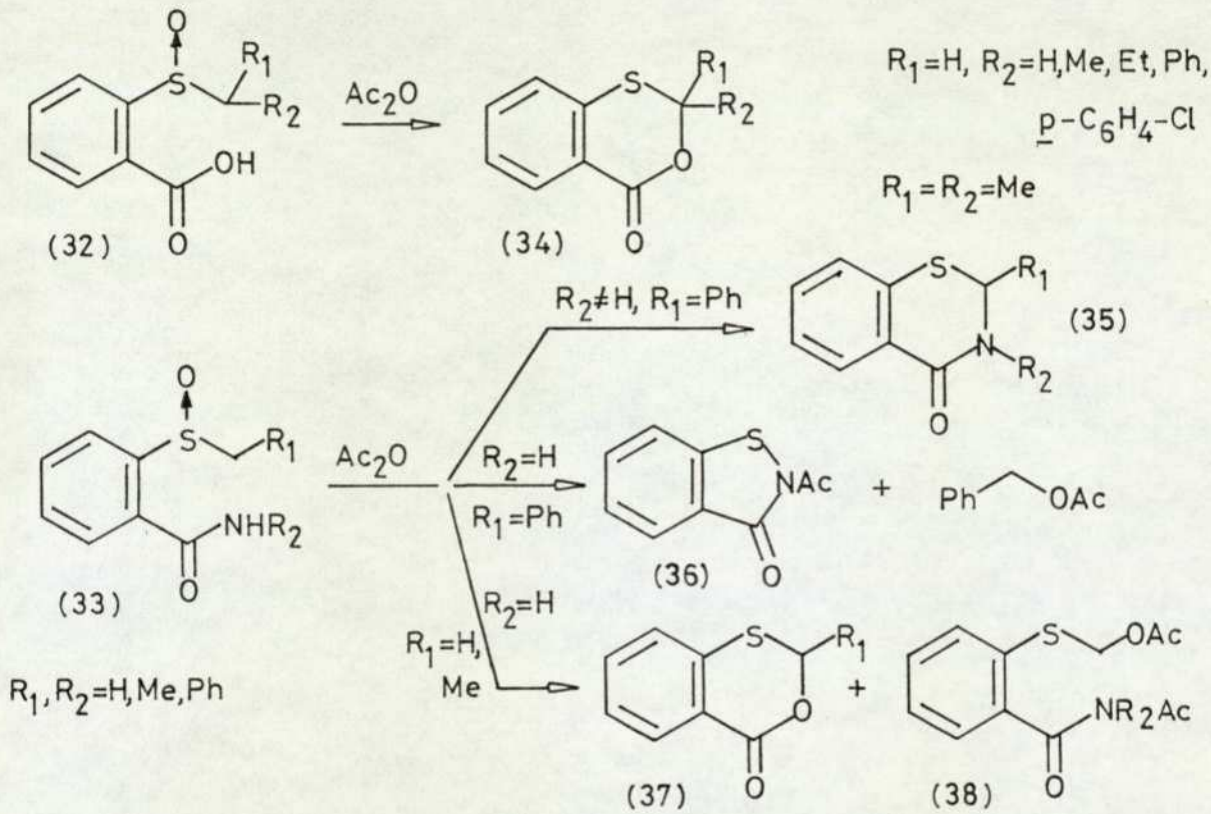
(30a) (31a)

(30b) (31b)

face as the S-O bond in the precursors was taken to imply an intramolecular transfer via an ion pair. The carbonium

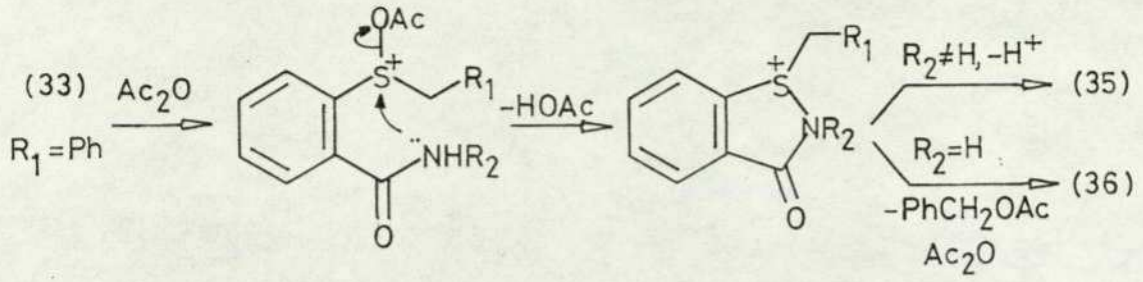
ion would be quenched very rapidly indeed. Nevertheless, the possibility of a 1,2-shift (Eqn. 6) or the cyclic rearrangement cannot be excluded.

Oae and Numata have investigated the reaction of o-carboxyphenyl (32) and o-carbamoylphenyl sulphoxides (33).[13] The reaction was found to be highly efficient except for the



methyl and ethyl sulphoxides (33, R_1 = R_2 = H) and (33, R_1 = Me, R_2 = H). In the latter case "several other products [than (37, R_1 = Me)] could not be identified" and the methyl sulphoxide gave the normal, N-acetylated, Pummerer product (38) as the major component. Furthermore the N-methyl derivative (33, R_1 = H, R_2 = Me) furnished (38) and the desacetyl compounds only. Somewhat inconsistently, Oae formulated two different mechanisms (Eqn. 11 and Eqn. 12) to account for the formation of (36) and (37). The postulated mode of

formation of (34) (Eqn. 13) deserves additional comment in the light of subsequent publications.



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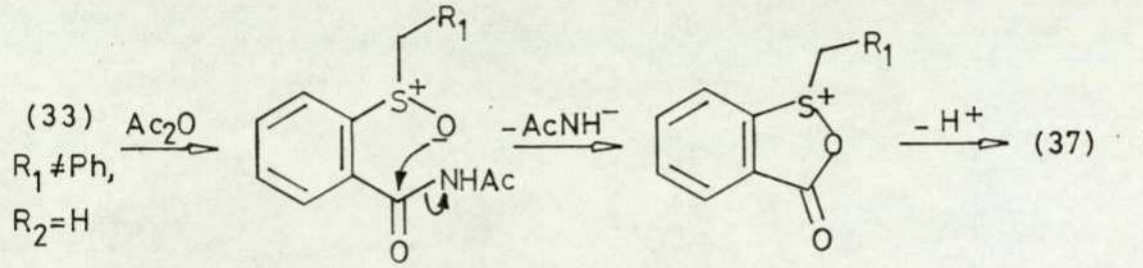
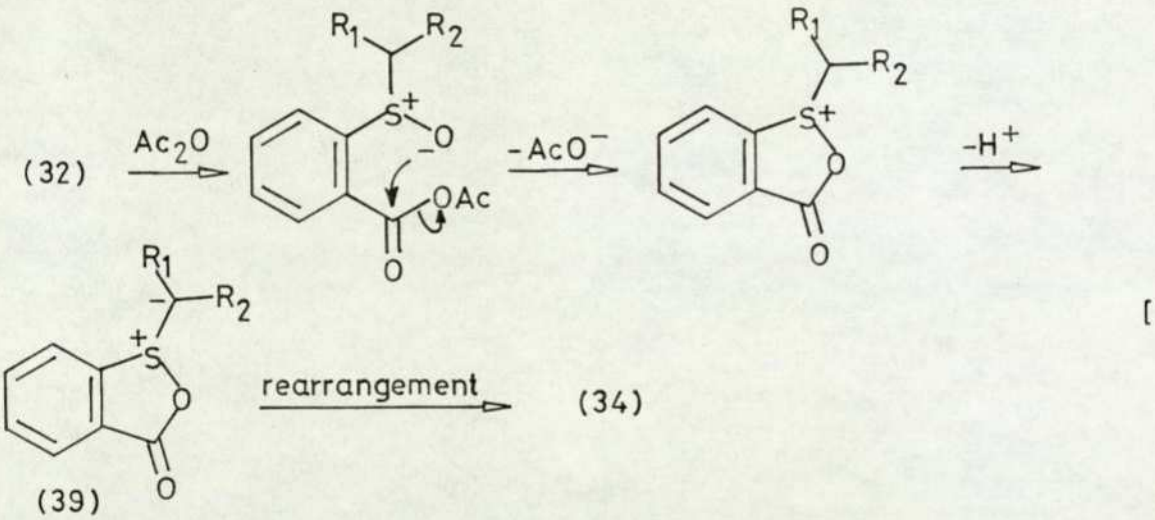
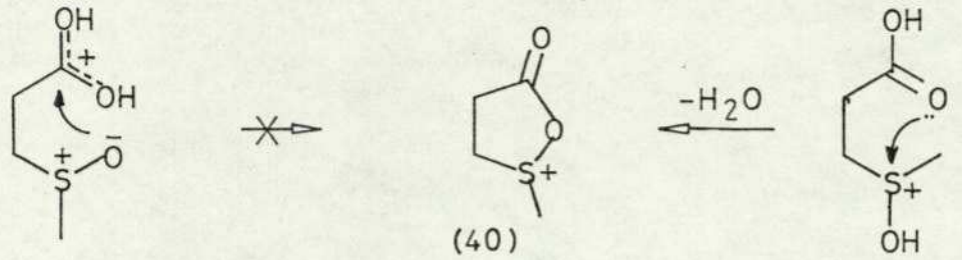


[12]



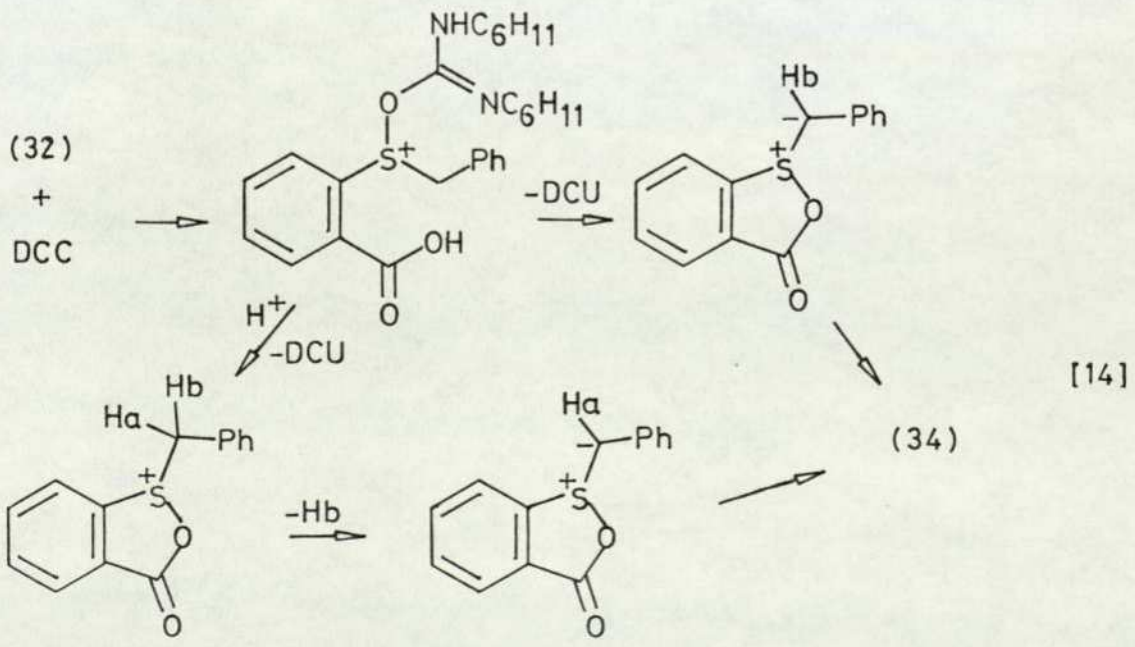
[13]

Oae has investigated this reaction in some detail.[14] Having labelled the sulphoxide oxygen he found that it was not incorporated into the ortho-carboxy group. The oxygen exchange and racemisation of sulphoxides has been well studied.[15] Two mechanisms were proposed, for sulphoxides featuring a suitably disposed carboxy group, leading to the cyclic acyloxy sulphonium ion (40).[16] However, Landini has shown, conclusively, that (40) is formed via nucleophilic



attack on the sulphoxide.[16b] Inexplicably, in view of his own data and apparently aware of Allenmark's work (vide infra) Oae persists with the mechanism of Equation 13 which requires that the sulphinyl oxygen should appear in the carboxy group. He rationalises the observed order of reactivity (iso-Pr > n-Pr > Me > CH_2Ph) by invoking the relative basicity of sulphoxide oxygen in the respective compounds, i.e. the attack of the oxygen on the acid anhydride is supposed to be the rate-determining step. The alternative explanation that the relative stabilities of the ylids (39) also follow the order of reactivity appears not to have been considered.

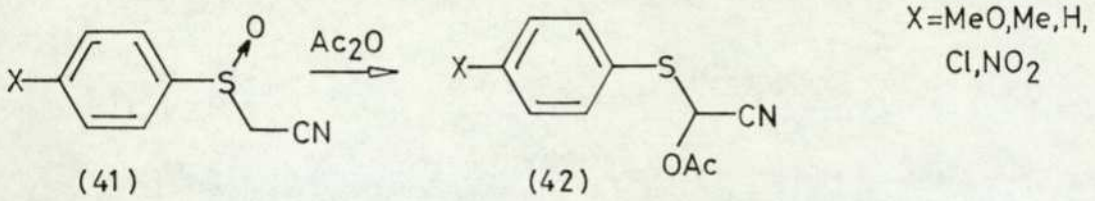
Allenmark and Stridsberg have, independently, discovered that the laevorotatory sulphoxide (32, R_1 = H, R_2 = Ph), on treatment with DCC and orthophosphoric acid gave the optically active sulphide (34).[17] The reaction was also found to be



[14]

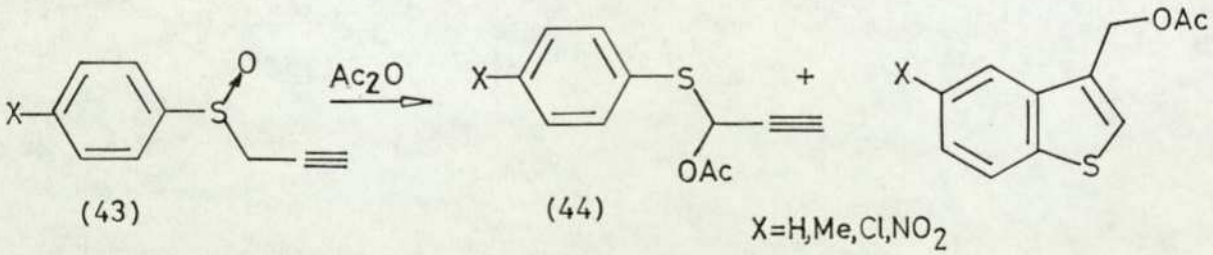
stereospecific in acetic anhydride[18] and the mechanism shown in Equation 14 was proposed. The two paths were invoked in order to explain the effect of added acid on the sign of rotation of the product.

Further examples of stereospecific rearrangements from Oae and co-workers have duly appeared. The reaction of an optically active cyanomethyl p-tolyl sulphoxide (41, X = Me) in acetic anhydride, gave a high yield of the sulphide (42)



(41) (42)

although the enantiomeric excess was low.[19] An experiment with the ^{18}O labelled sulphoxide seemed to indicate that the migration was intramolecular. A cyclic mechanism (cf. Eqn. 5) was apparently predominant. A similar study was performed with the aryl propargyl sulphoxides (43),[20] although the yields of the sulphides (44) were less impressive, owing to



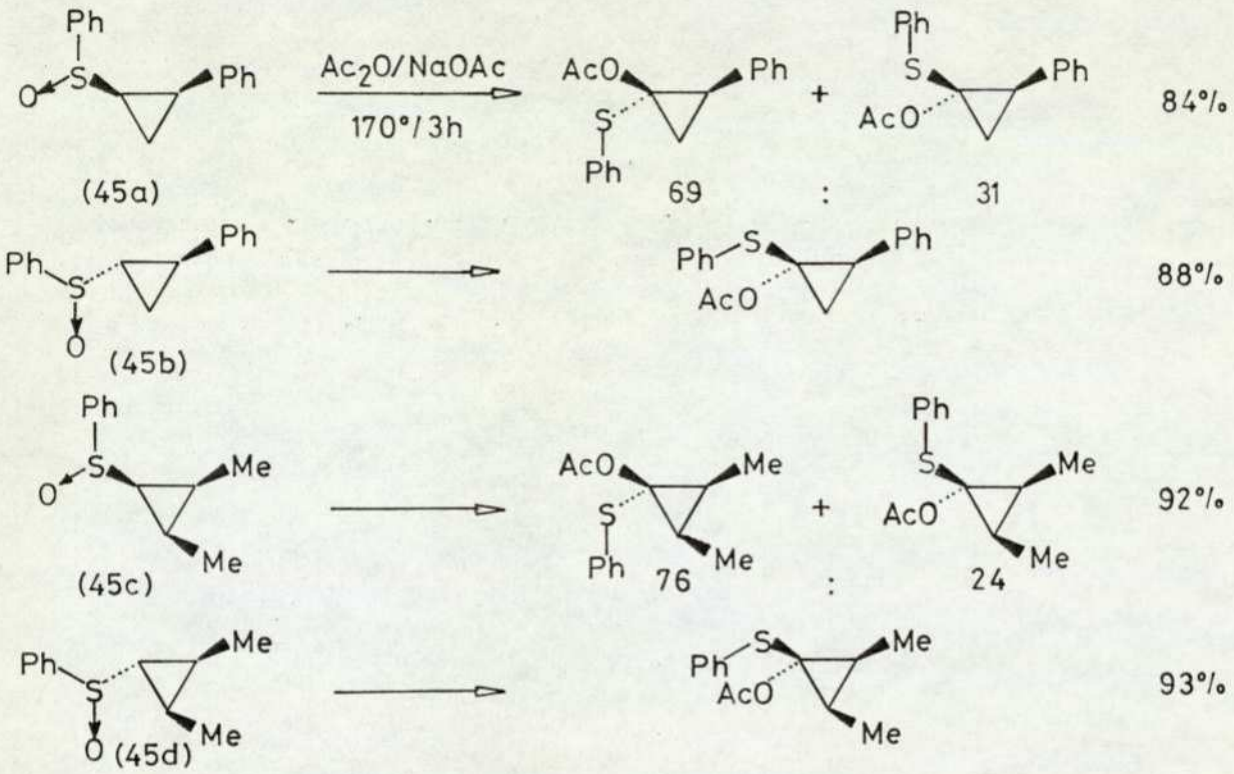
(43) (44)

the competing Thyagarajan rearrangement.

The dextrorotatory p-tolyl propargyl sulphoxide (43, X = Me) gave the optically active sulphide (44, X = Me). Although the rotation of the product was low ($[\alpha]_D$ + 2.2) the reaction was considered to be highly stereospecific since the recovered sulphoxide had undergone 91% racemisation.

From an experiment with labelled oxygen, the migration was again judged to be predominantly intramolecular but, this time, the 1,2-shift (cf. Eqn. 6) seemed to be the major mode.

The reaction of 1-phenylsulphinyl cyclopropanes (45) was also found to be stereoselective.[21] The absence of ring opened products was taken to imply that the rearrangement did

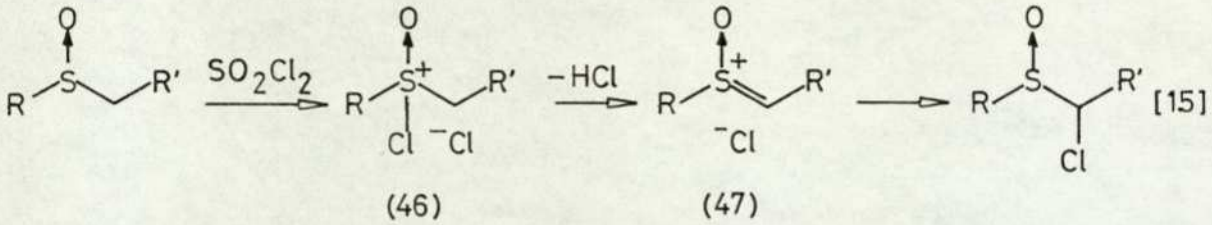


not proceed through the carbonium ion intermediate. The isomerisation observed in the cis- (45a) and the cis-, syn- (45c) compounds was attributed to steric crowding, but the mechanistic implications were not discussed.

The acetic anhydride treatment of sulphoxides, with alkyl chains other than the lowest homologs, frequently yields vinylic sulphides.[4,9,22] It is not clear whether these arise through the abstraction of a proton from the sulphur-stabilised cation, or via the elimination of acetic acid from the primary product. The apparent elusiveness of

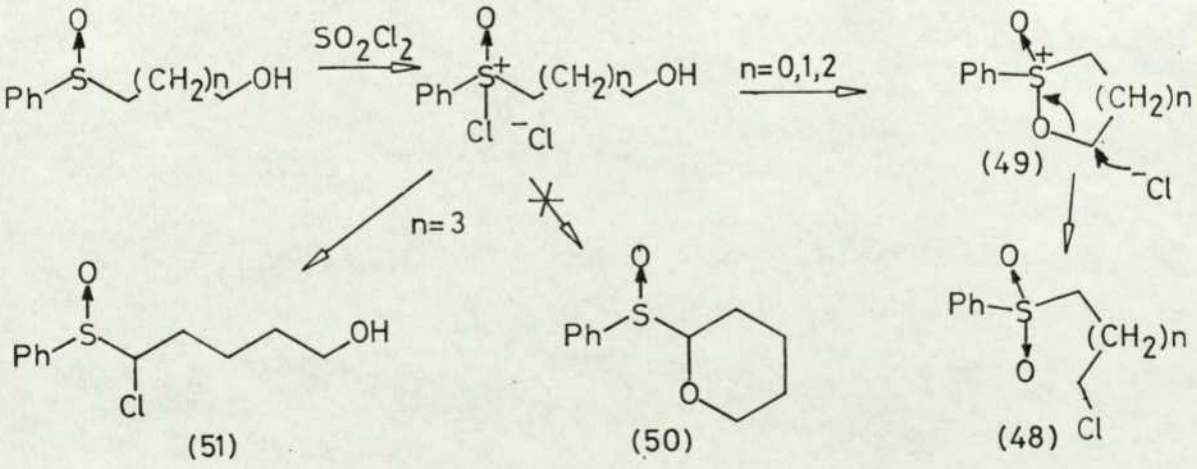
the carbonium ion[8,21] suggests that the latter alternative is more likely. In contrast, halogenation of sulphides has been shown to occur via the cation.[23] This reaction, which involves a chlorosulphonium salt as an intermediate, apparently gives products where the migration has occurred to the more highly substituted carbon.[24]

The related chlorination of sulphoxides is also believed to proceed through the oxosulphonium ion (47) (Eqn. 15).[25] However, Durst was unable to demonstrate its discrete presence.[26] In an elegant study, he showed that sulphoxides



(46) (47)

bearing nucleophilic groups (e.g. hydroxy) in positions β, γ and δ to the sulphoxide function gave high yields of the chloro sulphones (48). Thus, the chloro-oxosulphonium salt (46) is readily trapped by nucleophiles to give the cyclic



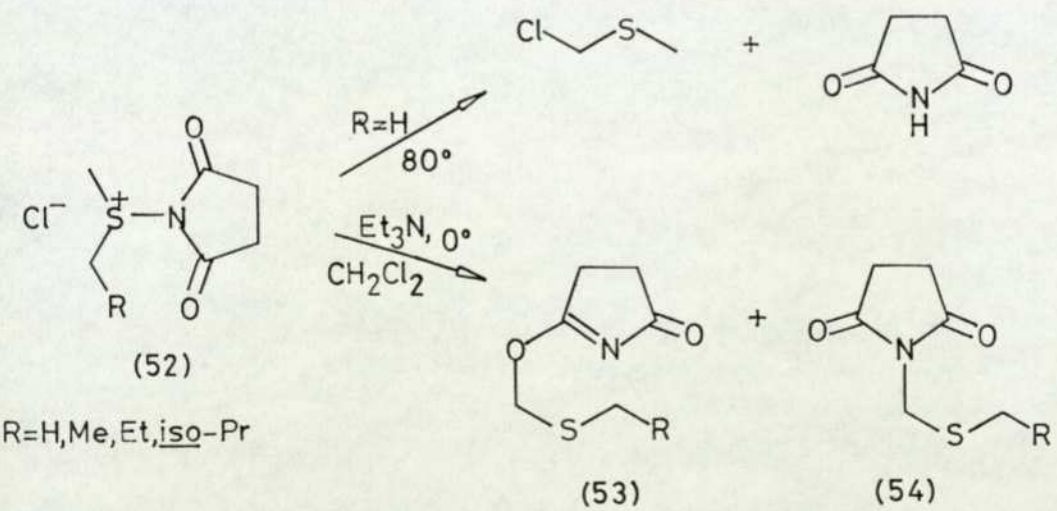
salt (49) and eventually (48). However, with n = 3 the tetrahydropyran (50) was not observed. Despite the favourable

disposition of the hydroxy group the presumed ion (47) was not trapped; α-chloro sulphoxide (51) was obtained in good yield.

The general, though not very helpful, picture that seems to emerge is that, the exact mechanism of the Pummerer rearrangement is very sensitive to the reaction conditions as well as to subtle structural changes in the substrates.

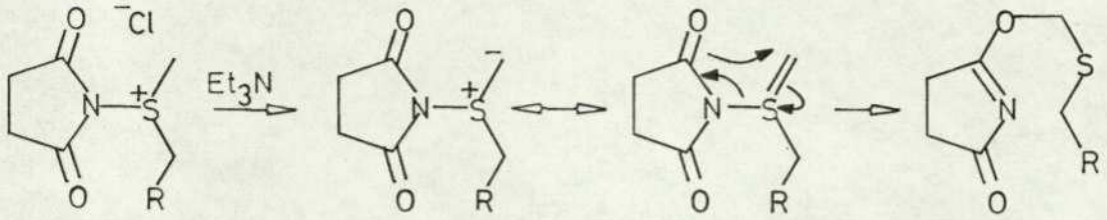
Reactions related to the Pummerer rearrangement

α-Chlorination of sulphides with N-chlorosuccinimide was, originally, thought to proceed via the chlorosulphonium salt.[24] However, Vilsmaier and Sprügel have shown that the reactive species is in fact the succinimidyl sulphonium salt (52), which, on heating, gives the Pummerer product.[27] It



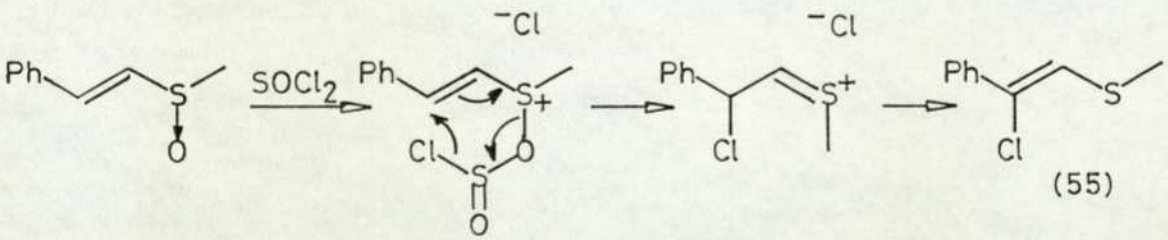
(52) (53) (54)

was further shown that the complex (52) on treatment with triethylamine gave high yields of the O-alkylated imide (53).[28] Since unsymmetric salts (52) gave exclusively products of migration to the least substituted carbon, Vilsmaier formulated a Stevens-type mechanism (Eqn. 16). However, the

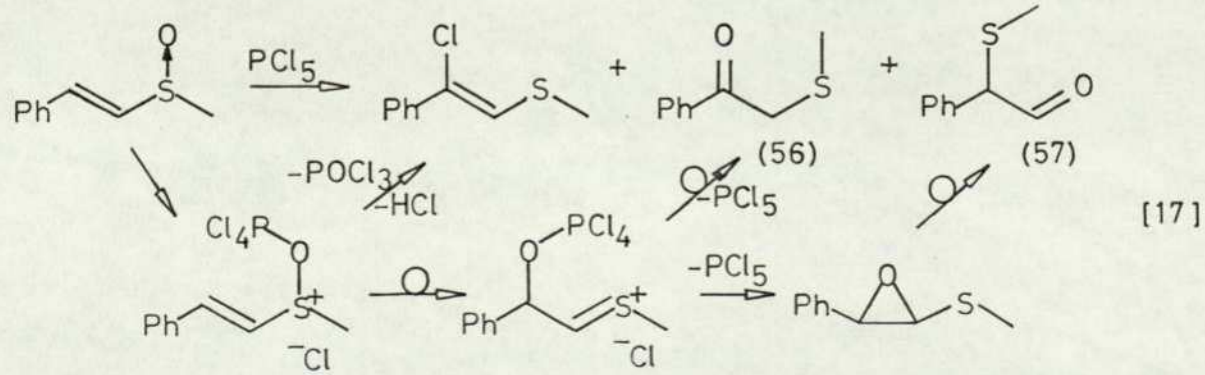


appearance of the N-alkylated product (54), albeit in small amounts, suggests that an ion-pair mechanism cannot be excluded. Secondary, acyclic amides can also be converted to the o-methyl-thio methyl imino ethers.[29] Treatment of these compounds with TFA readily regenerates the amide. The salt (52, R = H) can also be used to oxidise alcohols, in high yields, as was shown by Corey.[30]

In their original exploration of β-keto sulphoxide chemistry, Russel and co-workers have observed that methyl styryl sulphoxide, on treatment with thionyl chloride, gives the chlorosulphide (55), probably via the intermediates shown.[31]

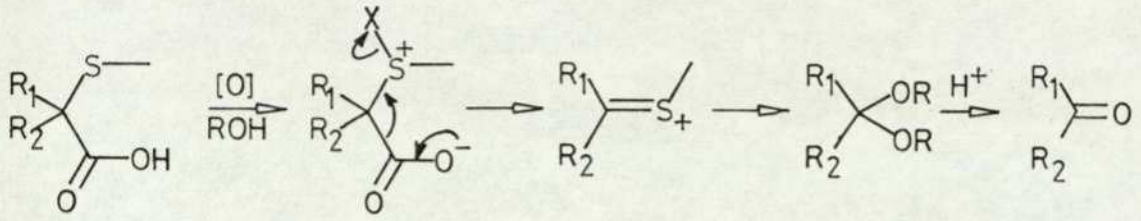


More recently, a Japanese group noted the unusual by-products (56) and (57) obtained in the chlorination of the same sulphoxide with phosphorus pentachloride.[32] Again a Pummerer-type



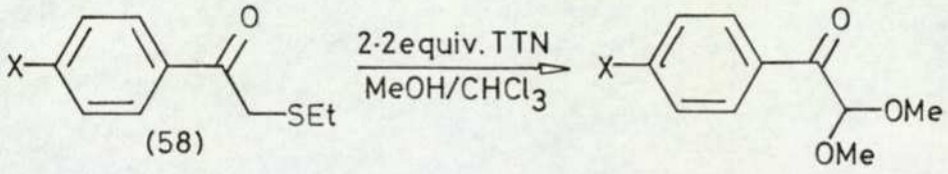
mechanism (Eqn. 17) was invoked.

The oxidative decarboxylation procedure developed by Trost (Eqn. 18) is also thought to involve the formation of a sulphur-stabilised carbonium ion.[33] The elimination of carbon dioxide is initiated by oxidising agents such as NCS,



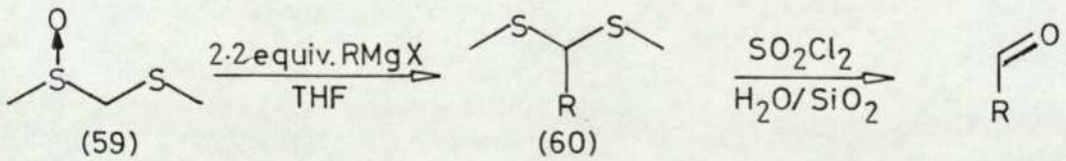
[18]

sodium metaperiodate etc. A cation radical has been suggested as a likely intermediate in the thallium (III) nitrate oxidation of α-thioethyl acetophenones (58).[34]



(58)

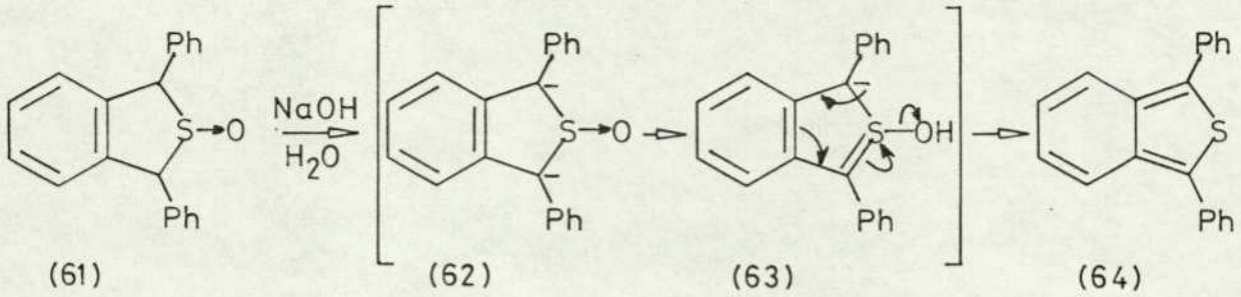
The action of Grignard reagents on methyl methylthiomethyl sulphoxide (59) is formally a Pummerer-type reaction,[35] although the mechanism was not discussed. The products (60)



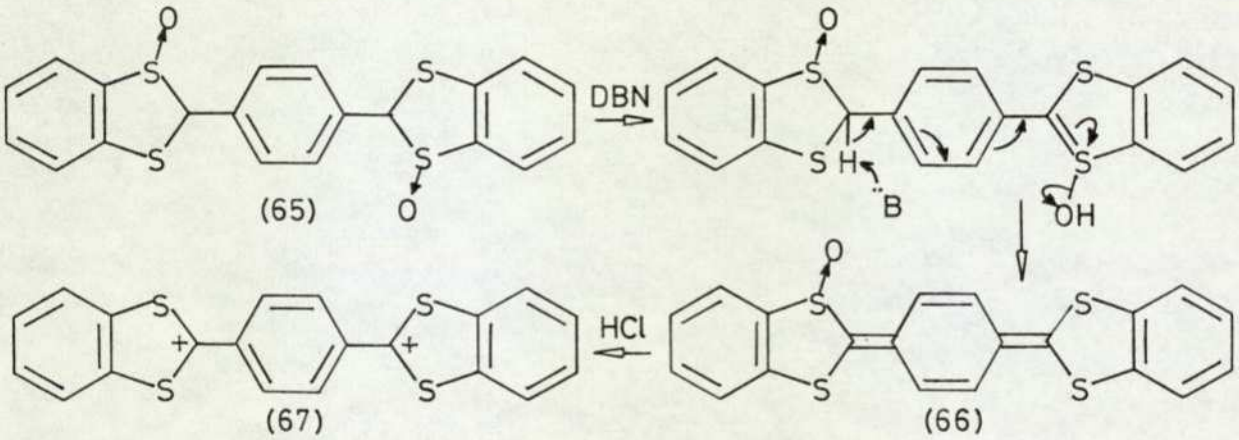
(59) (60)

can be efficiently converted to aldehydes with sulphuryl chloride and wet silica,[36] this time a normal Pummerer reaction. It is interesting to note that the former process is the "umpolung" version of the 1,3-dithiane synthesis of thioacetals.

An unusual base-catalysed dehydration of sulphoxides has been observed by Cava and co-workers.[37] For example, the sulphoxide (61) on boiling in aqueous sodium hydroxide gave



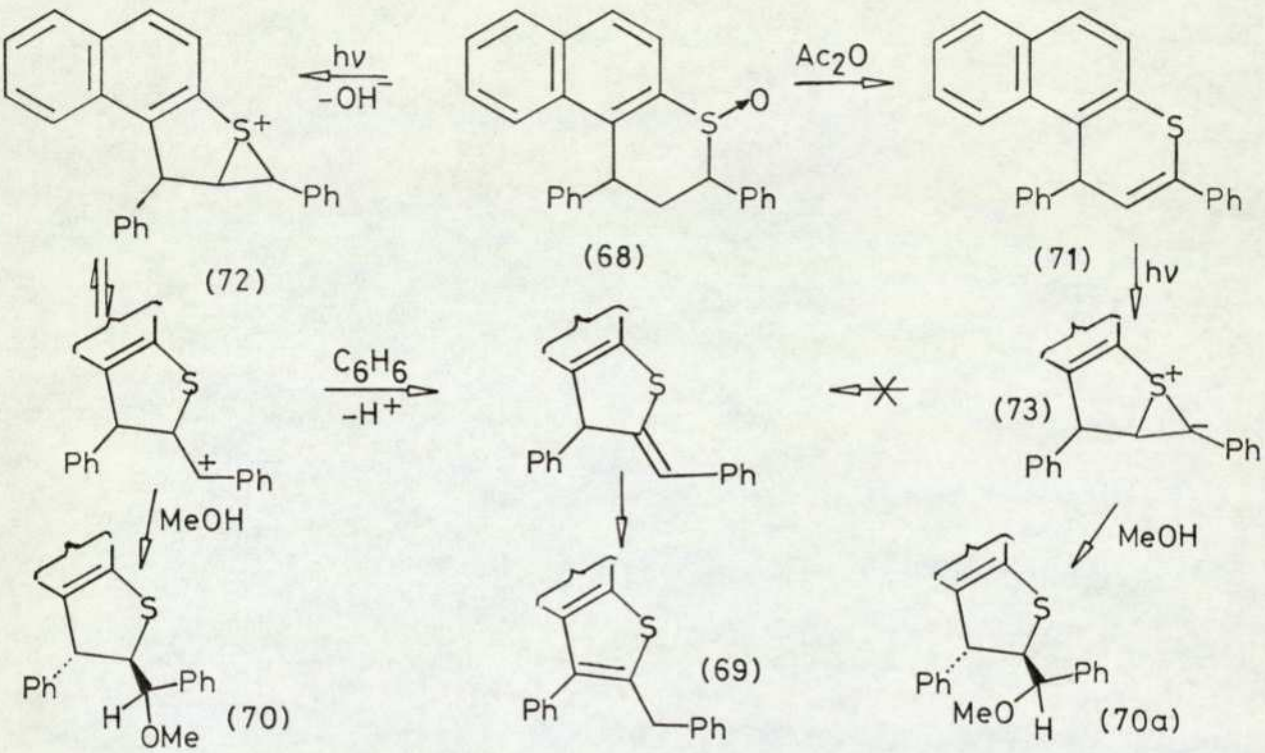
the benzo[c]thiophene. The dehydration was suggested to occur via the dianion (62) since the monoanion of (61) was stable. Protonation of the dianion (62), on oxygen, would then give the monoanion (63) which can expel the hydroxide ion. An equally intriguing reaction was observed with the disulphoxide (65), which on treatment with a strong base underwent



one dehydration to give the purple-black (66).[38] Addition of acid to the monosulphoxide (66) gave the yellow dication (67). These alkaline dehydrations, apart from being fascinating from a mechanistic view-point, should allow the preparation of similar highly acid sensitive compounds.

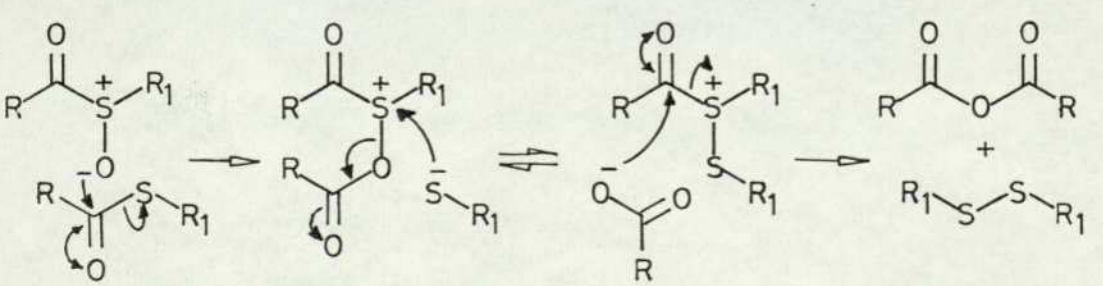
A reaction vaguely related to the Pummerer is the photo-induced dehydration of the sulphoxide (68). Schultz and Schlessinger[39] found that irradiation of (68) in an inert solvent gave the naphthothiophene (69). In the presence of methanol the dihydrothiophene (70) was formed. The inter-

mediacy of the Pummerer product (71) was ruled out since this vinyl sulphide did not give the thiophene (69). The sulphur-stabilised cation (72) was postulated as a likely precursor to both (69) and (70). Interestingly, irradiation of the



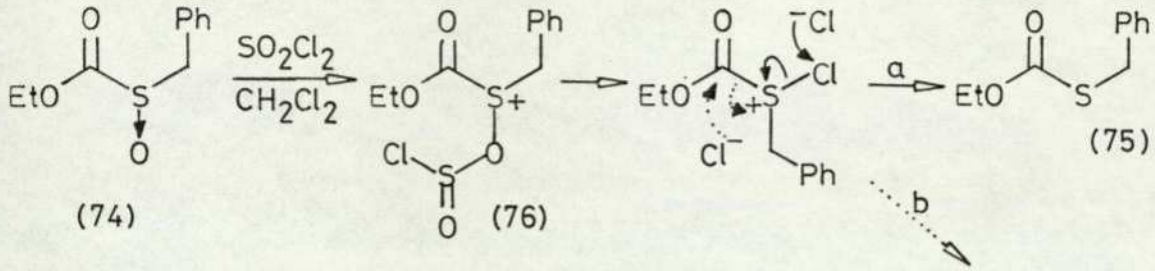
sulphide (71), in methanol, gave the diastereoisomeric dihydrothiophene (70a).[40] In this case the ylid (73) was thought to be the intermediate. Schultz pursued this reaction further and developed a useful dihydrothiophene synthesis.[41]

The oxidation of thiol esters is believed to involve the S-oxide as an intermediate,[42] which reacts with the starting material as proposed by a Portugese group (Eqn. 19).[43] Support for this mechanism comes from the observation that



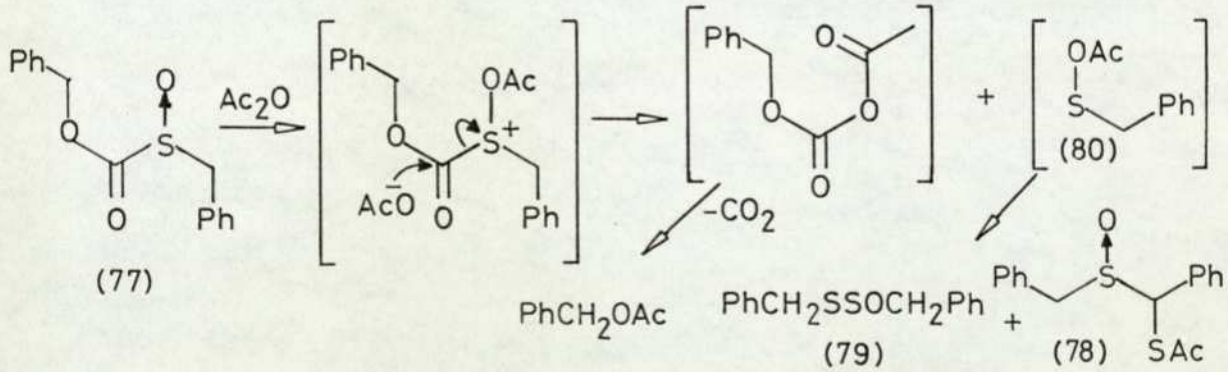
[19]

ethoxycarbonyl benzyl sulphoxide (74) reacts with thionyl chloride to give the thiocarbonate (75), ethyl chloroformate and the disproportionation products of, presumably, hydrolysed benzylsulphenyl chloride. The Pummerer-type salt (76) could

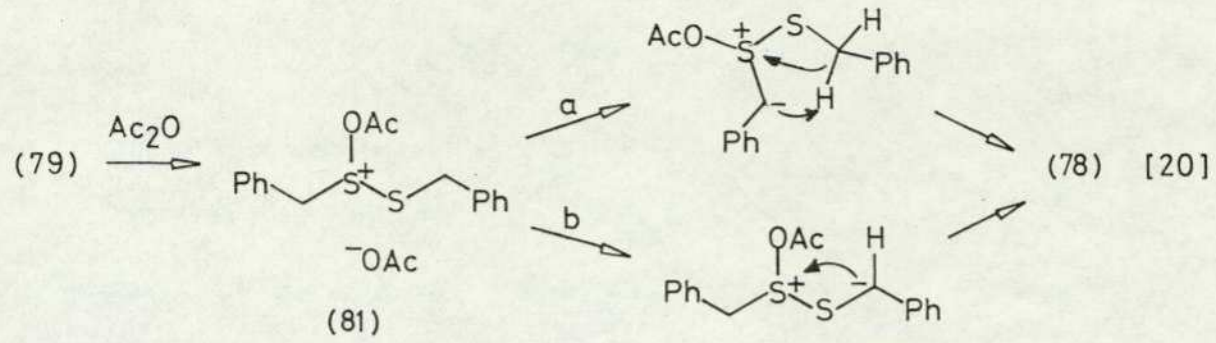


$PhCH_2SO_2SCH_2Ph + PhCH_2SSOCH_2Ph + (PhCH_2S)_2 \leftarrow [ClSCH_2Ph] + ClCO_2Et$

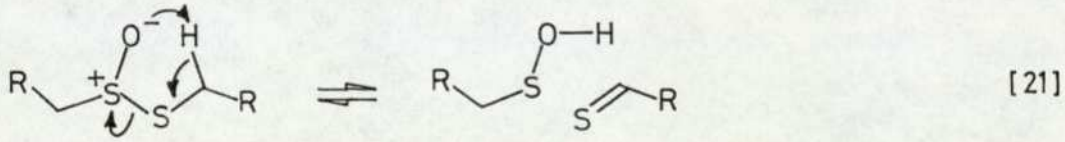
be trapped as a tetrafluoroborate which decomposed via path b only, since the thiocarbonate was not observed. Oae subsequently investigated the reaction of the sulphoxide (77) with acetic anhydride.[44] The major products were benzyl acetate and the sulphoxide (78) together with trace amounts of the thiosulphinate (79). A mechanism analogous to that



proposed by the Portugese workers was accepted. Oae then reacted the thiosulphinate (79) with acetic anhydride and observed the formation of compound (78), though in lower yield. This led to the conclusion that (79) was the intermediate, in the conversion of (77) to (78), and two mechanisms were suggested (Eqn. 20). Pathway (a) was

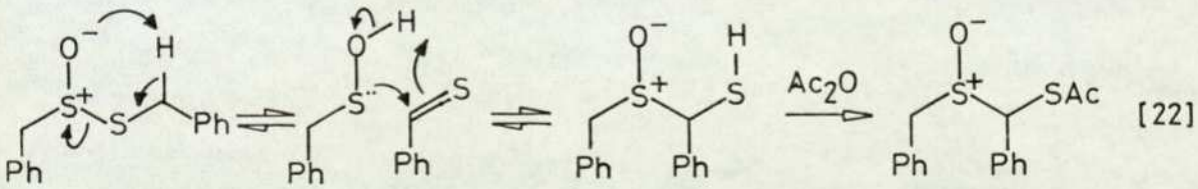


discarded on the basis of experiments with deuterium labelled (79), leaving the less likely route (b), which requires abstraction of the least acidic proton. Another Japanese group has shown that thiosulphinates give Pummerer products on heating in methanol alone.[45] Furthermore, Block, in a detailed study, has demonstrated that these compounds readily decompose to sulphenic acids and thioaldehydes (Eqn. 21).[46] These facts suggest that the conversion of (79) to (78) via



[21]

a dissociation-recombination mechanism, e.g. (Eqn. 22), is a more likely process. Another possibility could be that the

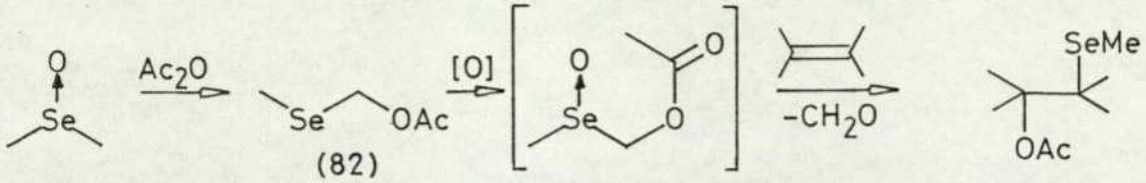


[22]

salt (81) is cleaved by the acetate ion to give the mixed anhydride (80). Elimination of acetic acid would again give thiobenzaldehyde and hence the observed product.

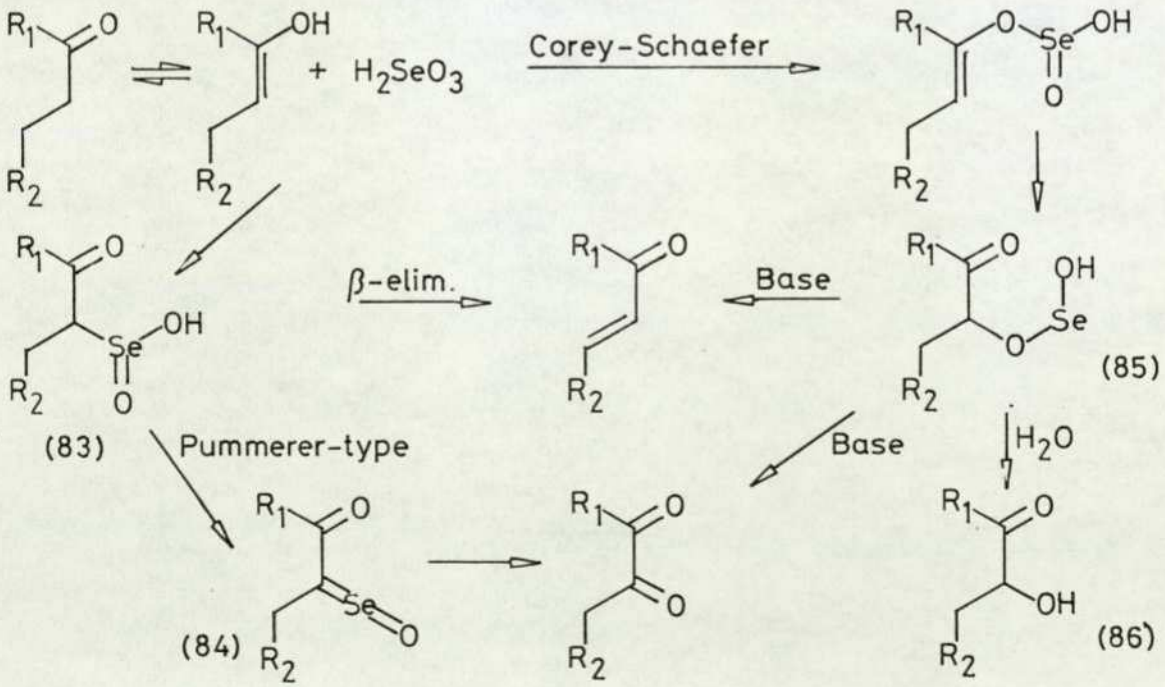
Simple selenoxides are also known to undergo the Pummerer

rearrangement. For example, dimethyl selenoxide on treatment with acetic anhydride gives the α-acetoxy selenide (82).[47] Further oxidation of (82) generates a reagent which adds to



olefins, in the Markovnikoff sense. Formaldehyde is the other product. The Pummerer reaction has not been observed with selenoxides possessing β-protons, which is not surprising in view of their ready fragmentation.

Recently, Sharpless and Gordon have presented substantial evidence implicating a Pummerer-type mechanism in the oxidation of ketones with selenium dioxide.[48] The hypothetical selenine (84) was suggested as a likely intermediate in the transformation of the β-keto seleninic acid (83) to the α-diketone.

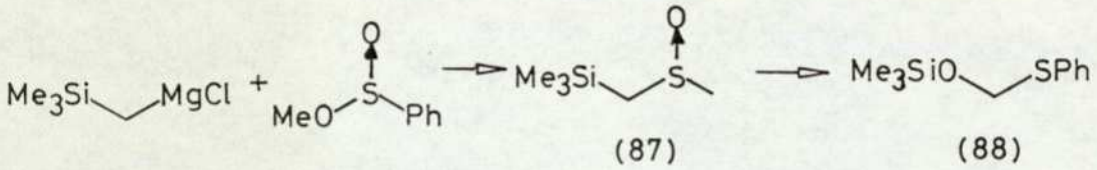


The main objection to the previously accepted mechanism (Corey-Schaefer) was that selenium esters, such as (85), are

rapidly hydrolysed to the ketols (86) and Corey had already shown that the latter were not intermediates. The formation of an intermediate β-keto seleninic acid also helps to explain unusual by-products in the oxidation of cyclic ketones with selenium dioxide/hydrogen peroxide.[48]

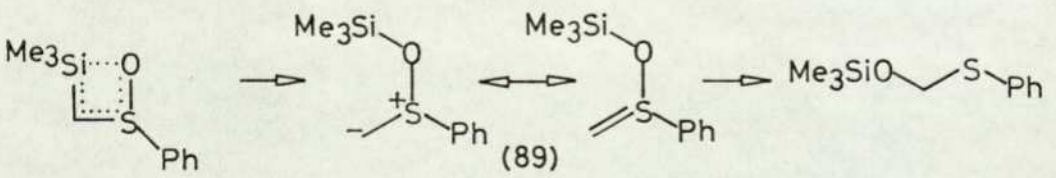
Sila-Pummerer Rearrangement

A decade ago, Brook described a synthesis of the novel trimethylsilylmethyl phenyl sulphoxide (87).[49] The compound was highly unstable, hence the unconventional preparation,



(87) (88)

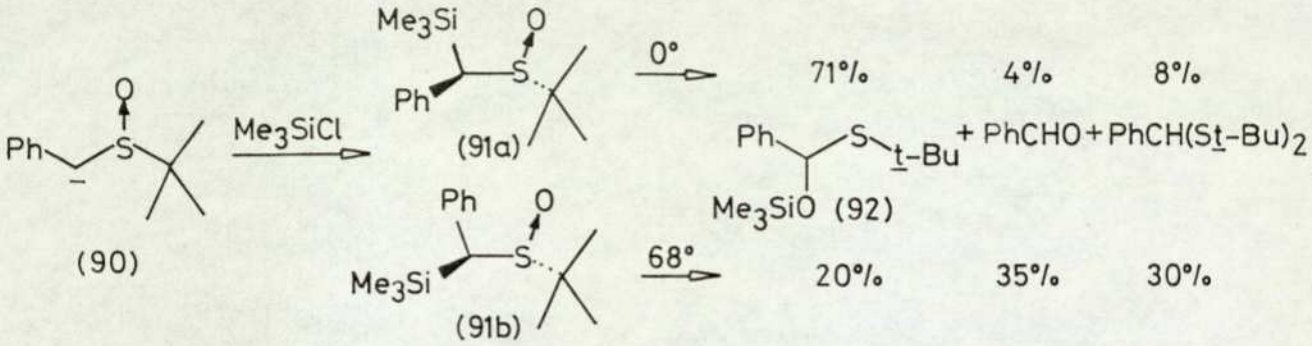
decomposing at room temperature to the α-siloxy sulphide (88). The sulphoxide (87) is relatively stable at low temperatures and can be deprotonated by strong bases.[50] The anion thus formed is a powerful nucleophile and will attack ketones and aldehydes to give vinyl sulphoxides, although the reaction appears to be limited to non-enolisable substrates. The rearrangement to sulphide (88) is thought to involve the transfer of silicon to the sulphinyl oxygen, via a four-



[23]

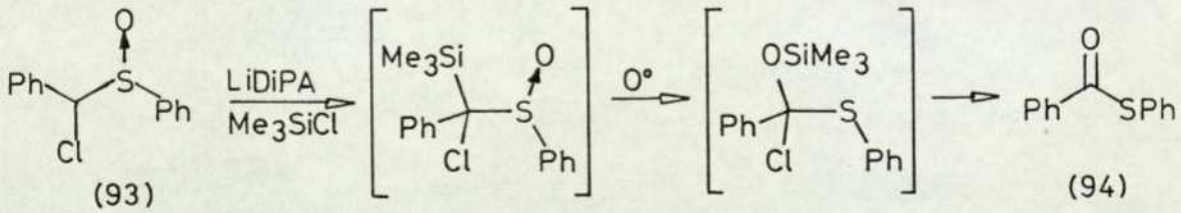
membered transition state.[51] The resultant ylid (89) would then rearrange, in the usual Pummerer manner, to the observed product (Eqn. 23).

The existence of the four-membered transition state was underlined by the recent results of Vedejs and Mullins.[52] They found that inverse addition of the lithium salt of the sulphoxide (90) to trimethylsilyl chloride gave two diastereoisomeric α-silylated compounds. The isomer (91a) could not be isolated since it rearranged above 0^{o} to the α-siloxy

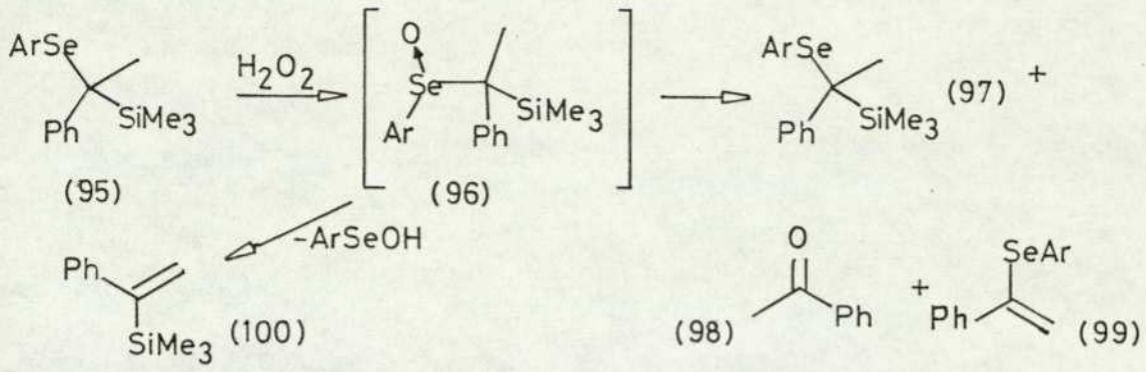


sulphide (92). The diastereoisomeric (91b) had to be heated and gave a much larger percentage of the disproportionation products. Presumably the latter compound cannot readily attain the co-planar arrangement of silicon and the sulphinyl oxygen.

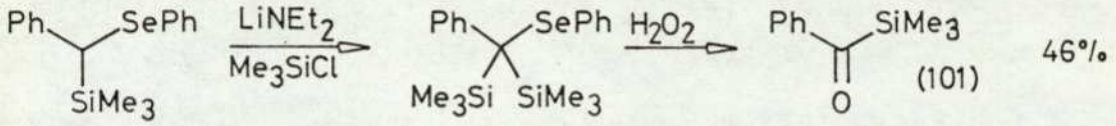
The anions of α-chloro sulphoxides such as (93), upon addition of trimethylsilyl chloride readily rearrange to the thiol esters (94).[53]



Selenium compounds are also prone to undergo the sila-Pummerer reaction. Reich[54] discovered that oxidation of the selenide (95) gave varying amounts of the products (97), (98) and (99) in addition to the desired vinyl silane (100). As



would be expected, the intermediate selenoxide (96) could not be isolated. However, the sila-Pummerer was advantageously

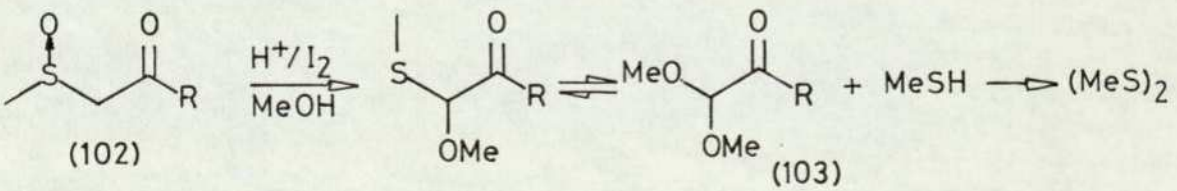


exploited to prepare the interesting silyl ketone (101).

Synthetic Applications

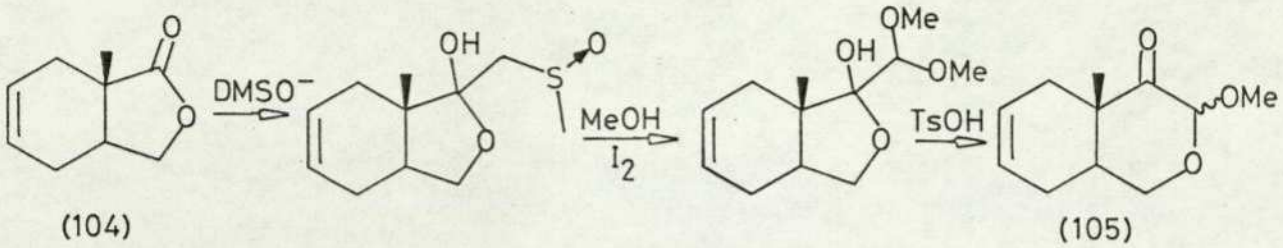
Since the pioneering work of Corey and Chaykovsky, and of Russel's group, the importance of β-keto sulphoxides, as synthetic intermediates, gained wide-spread recognition. This family of compounds undergoes the Pummerer reaction particularly readily, presumably due to the ease of formation of the intermediate ylid.

Simple β-keto sulphoxides (102) are rapidly converted to the acetals (103) in acidic alcoholic solutions.[55] High

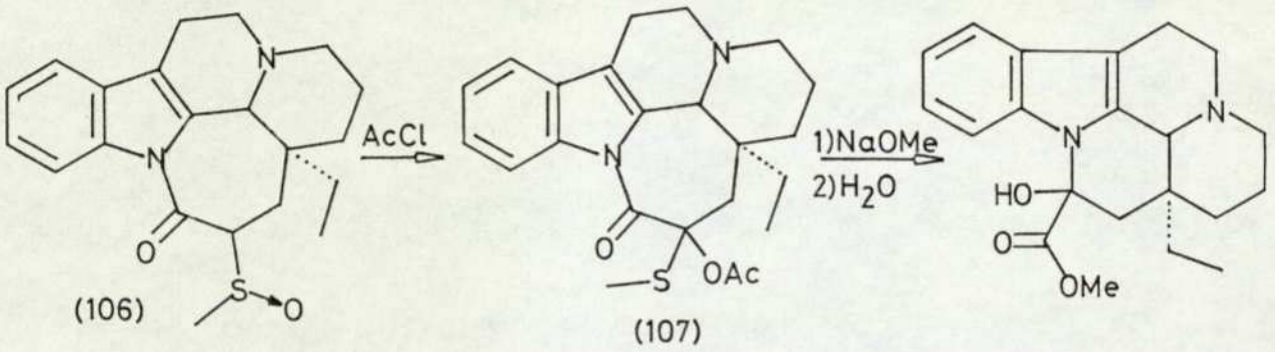


yields are obtained in the presence of iodine, since the released mercaptan is irreversibly oxidised to the disulphide,

thus driving a series of equilibria[56] to the ultimate product. Trost has made good use of these conditions in the key-step of the conversion of the lactone (104) to the acetal (105).[57]

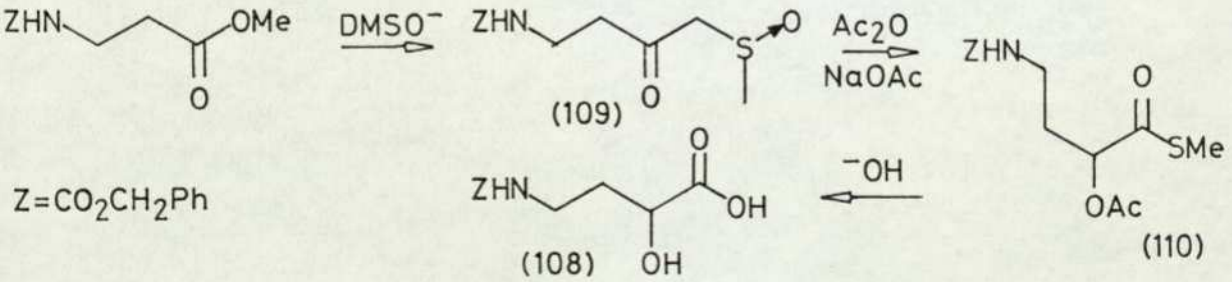


A recent synthesis of vincamine employed the Pummerer reaction to achieve the transformation of the sulphoxide (106)



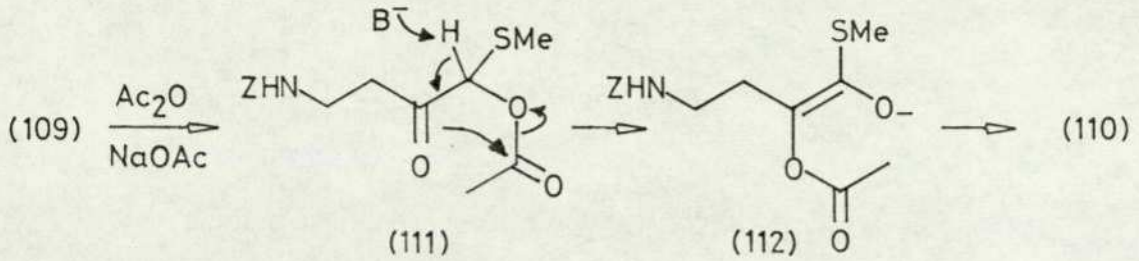
into the target alkaloid.[58] The presumed acetoxy sulphide (107) was not isolated.

Tsuchihashi and co-workers have made extensive use of the rearrangement of β-keto[59] and β-hydroxy sulphoxides.[60] For example, the N-protected 4-amino-2-hydroxybutyric acid

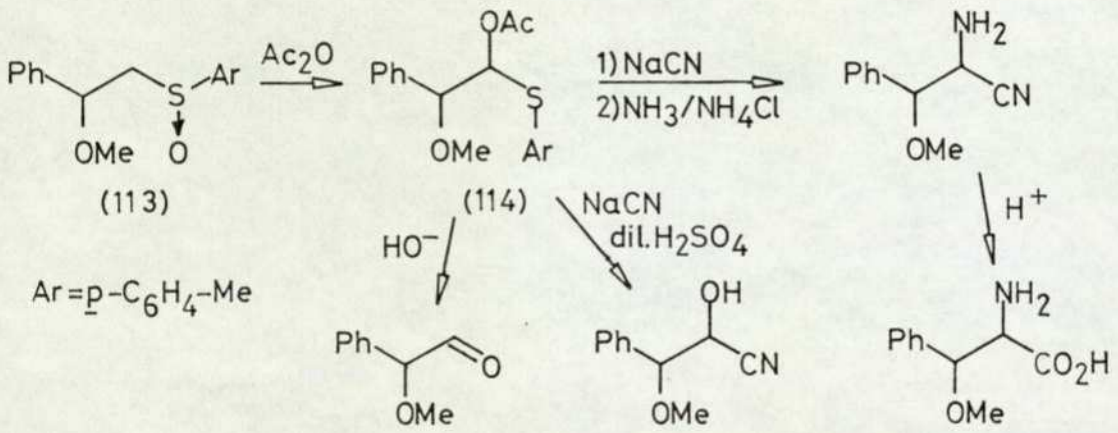


(108) was synthesised in three steps, in high yield, from N-benzyloxycarbonyl-β-alanine methyl ester.[59] The rearrangement of (109) to the thiol ester (110) is thought to involve

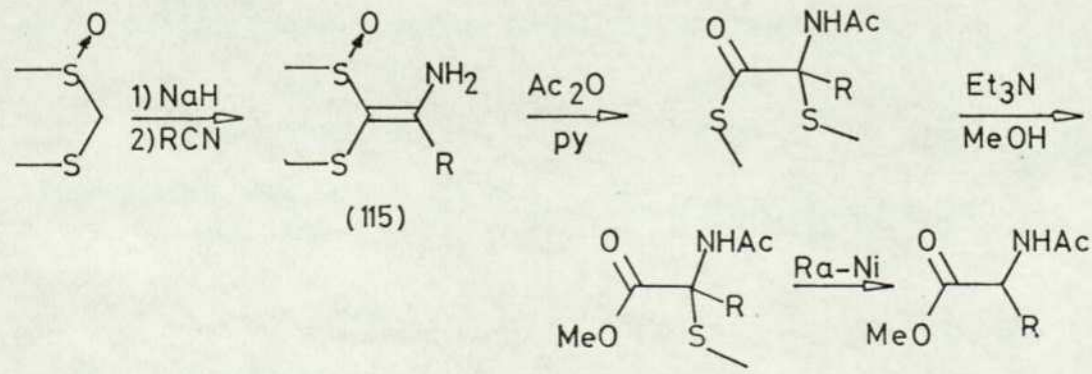
the usual Pummerer reaction, followed by internal oxidation-reduction of (111) with concomitant acetyl transfer to give



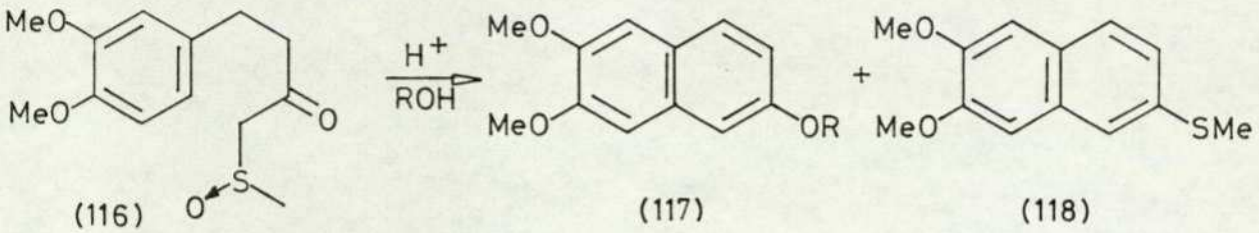
the enol (112). The conversion of β-hydroxy or β-alkoxy sulphoxides was equally efficient.[60] The rearrangement of 2-methoxy 2-phenylethyl p-tolyl sulphoxide (113) yields quantitatively the versatile synthetic intermediate (114).



Tsuchihashi has also developed a novel synthesis of amino acids starting with methyl methylthiomethyl sulphoxide.[61] Particularly noteworthy is the profound rearrangement of the enamino sulphoxide (115).

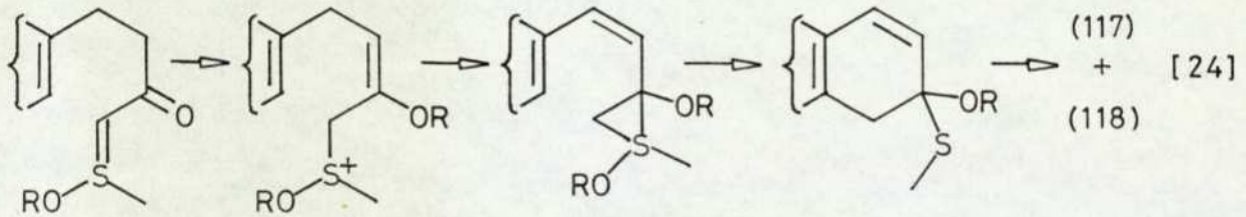


The intramolecular capture of the Pummerer intermediates has been explored by several groups. One example has already been mentioned in the Mechanism Section. Oikawa and Yonemitsu discovered that the keto sulphoxide (116), on treatment with tosic acid, cyclised to the naphthalene derivatives (117) and



(116) (117) (118)

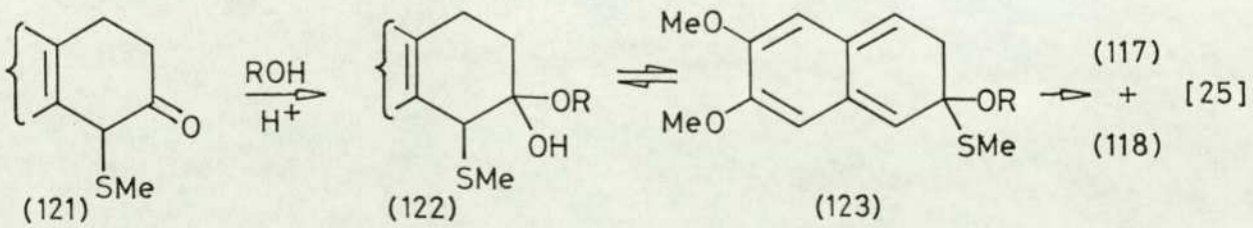
(118).[62] An unusual mechanism was invoked in order to account for the formation of the sulphide (118) (Eqn. 24). The



[24]

(119) (120)

initial alkylation of the sulphinyl oxygen was followed by acid-catalysed rearrangement, via the sulphurane (119), to the dihydronaphthalene (120). A more conventional mechanism (Eqn. 25) was suggested following the isolation of the inter-

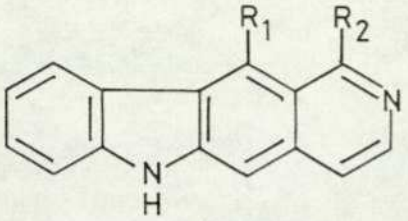


[25]

(121) (122) (123)

mediate keto sulphide (121).[63] The acetal (122) is presumably in equilibrium with the hemithioacetal (123). The Japanese workers have shown the generality of this reaction by

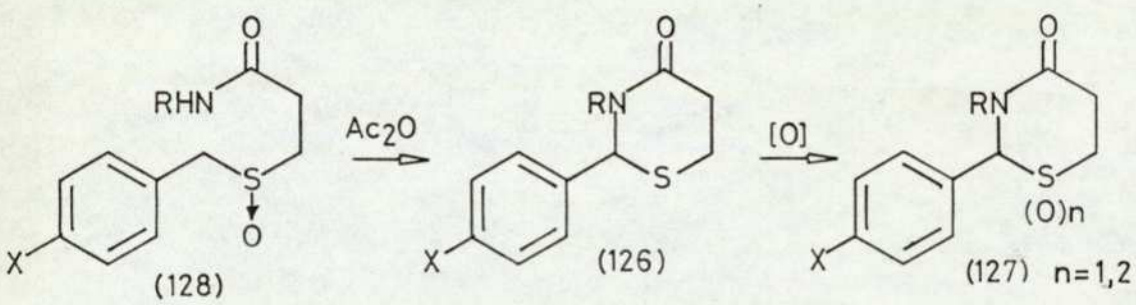
synthesising a wide range of fused heterocycles[64] including[65] olivacine (124) and ellipticine (125). An analogous approach has been utilised in the synthesis of pteridines,[66] 3(2H)-



(124) R_1=H,R_2=Me

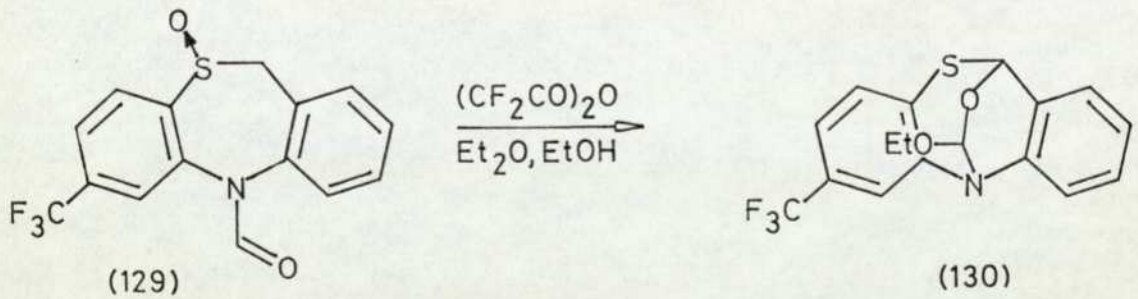
(125) R_1=Me,R_2=H

benzofuranones and 1,2-dihydro-indol-3-ones.[67] The cyclic amide (126), a key precursor in the synthesis of important



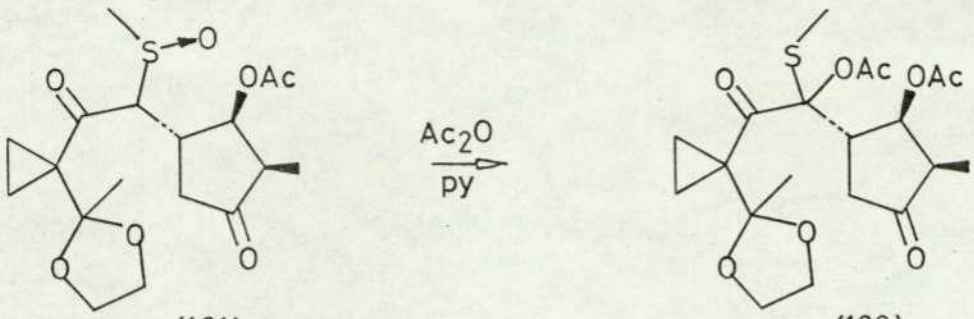
(128) (126) (127) n=1,2

muscle relaxants (127), was efficiently prepared by the intramolecular rearrangement of the readily available sulphoxide (128).[68] The aldehyde function of the thiazepine



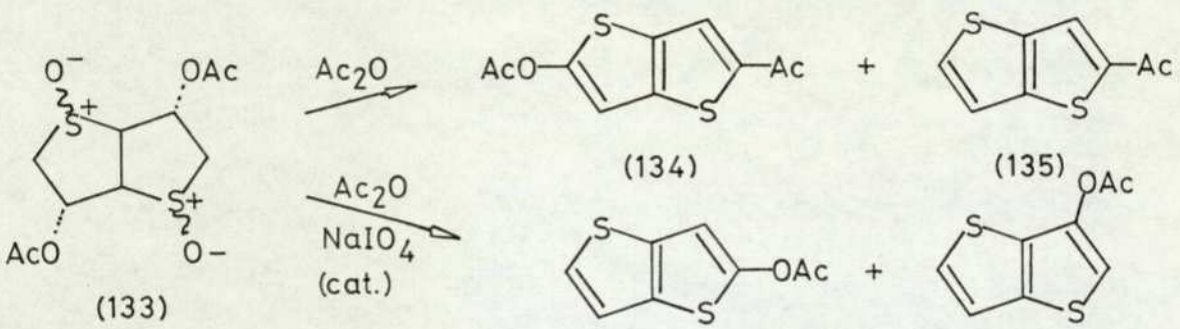
(129) (130)

(129) successfully trapped the Pummerer intermediate yielding the unusual bicyclic system (130).[69] The elaborate keto sulphoxide (131) was smoothly and stereoselectively converted to the acetoxy sulphide (132),[70] clearly illustrating the mildness of the reaction conditions. The reaction has been



(131) (132)

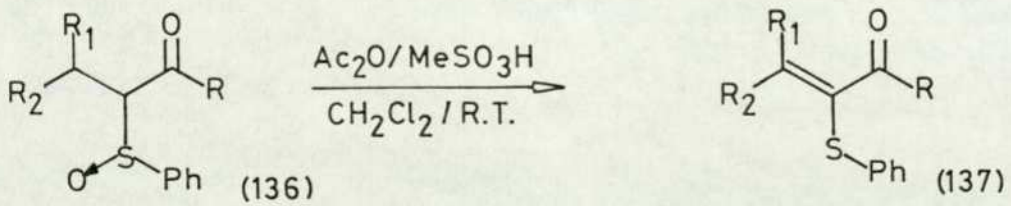
frequently used in the preparation of useful thio-sugars.[71] An interesting example is the extensive rearrangement of the disulphoxide (133).[72] Depending on the conditions employed,



(133) (134) (135)

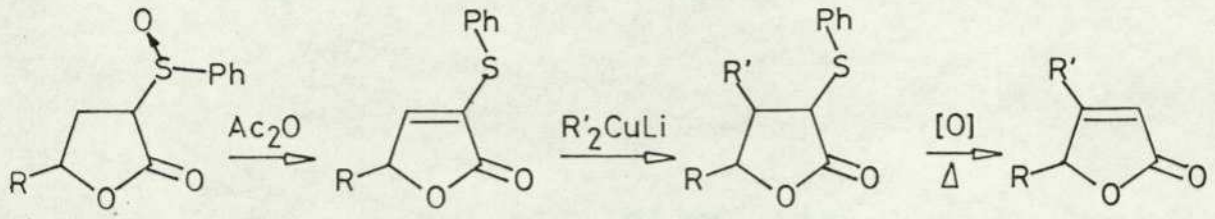
either of the thieno-thiophene pairs was obtained. The thiophenes (134) and (135) were thought to arise via acetylation of an ylid intermediate.

An alternative reaction of β-keto sulphoxides such as (136), i.e. dehydration, provides a valuable method for the synthesis of vinyl sulphides.[73] The unsaturated keto-



(136) (137)

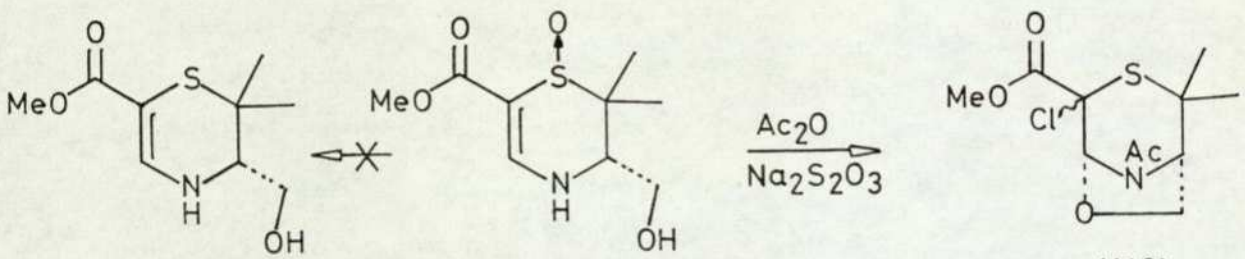
sulphides (137) are excellent Michael acceptors.[74] The presence of a β-carbonyl sulphide in the adducts allows for further elaboration, as illustrated for the synthesis of the butenolide (138).[75]



(138)

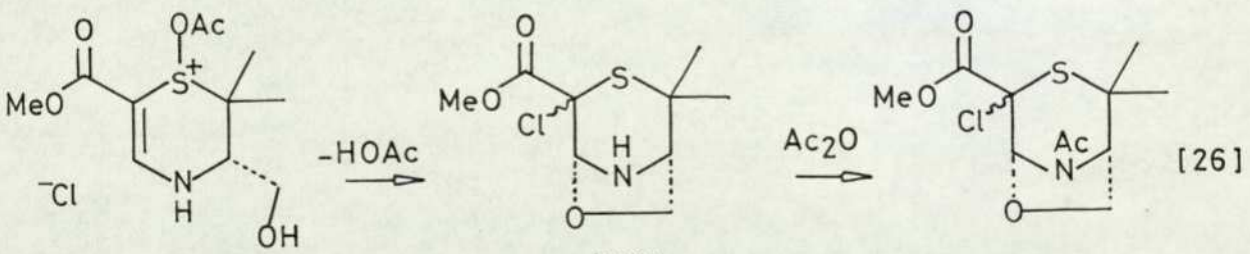
Additive and Vinylogous Pummerer Reaction

In 1972 Kitchin and Stoodley reported a novel rearrangement of the thiazine S-oxide (139).[76] An attempted reduction of (139), with sodium dithionite and acetyl chloride, gave



(141) (139) (140)

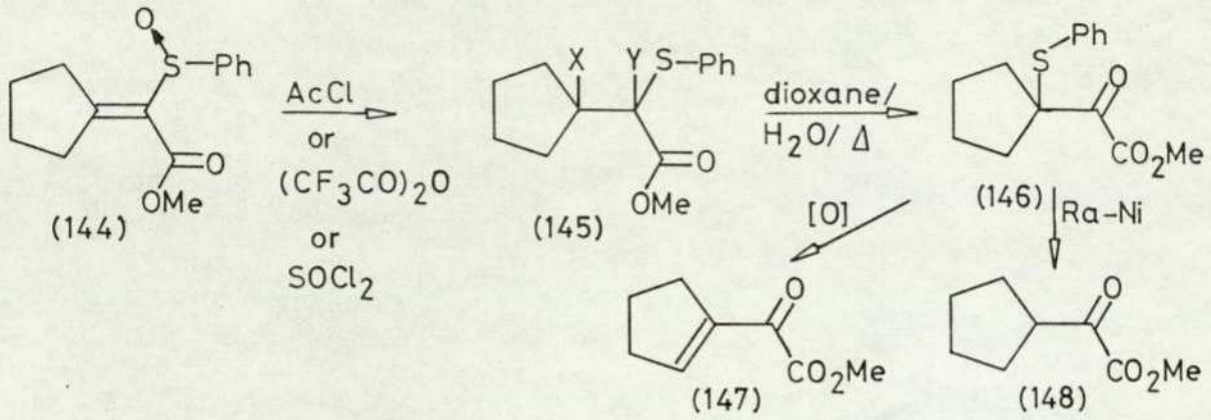
the bicyclic chloro sulphide (140) instead of the expected thiazine (141). Control experiments established that the dithionite ion did not play a part in this reaction, and that the unstable amine (142) was an intermediate. The salt (143) was thought to be the initially formed species (Eq. 26).



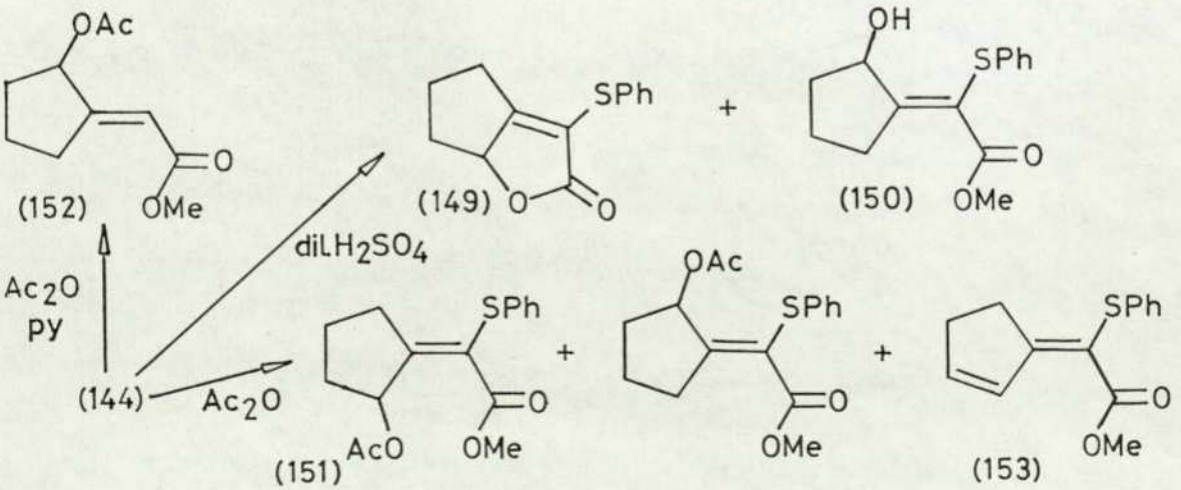
(143) (142) [26]

This additive rearrangement appears to be a general reaction of vinyl sulphoxides possessing an "activated" double bond.[81,77,82] Uda and his group have investigated, in detail, the transformations of methyl cyclopentylidene phenyl-

sulphinylacetate (144).[78] Treatment of the sulphoxide (144) with acetyl chloride, trifluoroacetic anhydride or thionyl chloride gave the corresponding sulphides (145) in high yield.

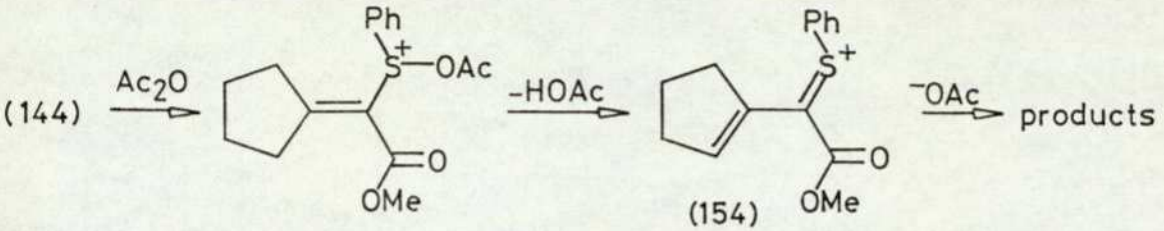


The chloro-acetoxy product (145, X = Cl, Y = OAc) and the ditrifluoroacetoxy compound (145, X = Y = $OCOCF_3$) were quantitatively converted to the phenylthio glyoxylate (146). The dichloro sulphide (145, X = Y = Cl), however, proved totally inert in refluxing aqueous dioxane. The phenylthio compound (146) could be further modified to the glyoxylates (147) and (148). The ester sulphoxide (144) underwent an apparently different rearrangement on treatment with dilute sulphuric acid.[79] The lactone (149) was the major component. Only



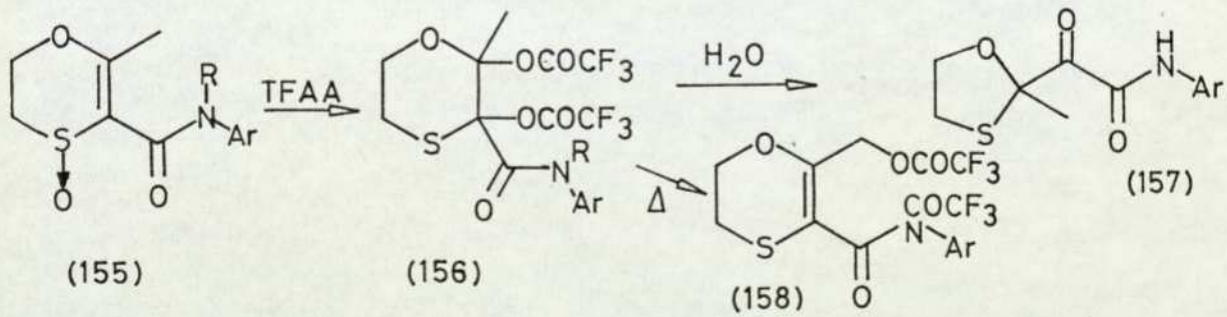
traces of the hydroxy ester (150) were formed. The reaction

with acetic anhydride gave three products. Again the predominant isomer (151) resulted from the oxidation of the carbon cis- to the ester. At higher temperatures the dienoic ester (153) became the sole product. This vinylogous rearrangement was rationalised by involving the sulphur-stabilised cation (154) as an intermediate, although this interpretation has been questioned.[81]



The reaction in acetic anhydride and pyridine gave the acetoxy ester (152) as the only product. The exclusive formation of only one isomer is presumably due to the base-catalysed isomerisation of the double bond, followed by the well known sulphoxide-sulphenate rearrangement.[80]

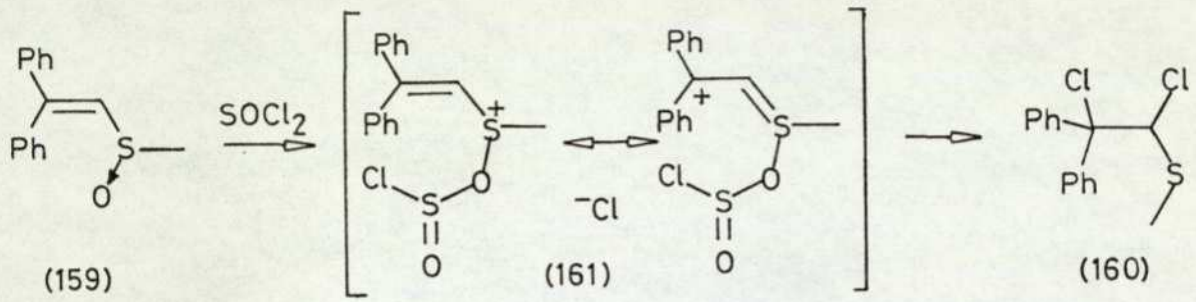
Equally interesting reactions were observed with carboxin sulphoxide (155).[81] Treatment with trifluoroacetic anhydride gave a high yield of the ditrifluoroacetoxy product



(156, R = H). An analogous result was obtained with the N-methyl derivative (155, R = Me). Mild hydrolysis of the secondary amide (156, R = H) gave the oxathiolane (157). On heating, the allylic trifluoroacetate (158) was formed. The

mechanism of this conversion was not discussed. However, the N-methyl analog (156, R = Me) did not rearrange under identical conditions.

The chlorination of the vinyl sulphoxide (159), with thionyl chloride, furnished the saturated sulphide (160),[82] unlike the reaction of methyl styryl sulphoxide (page 26). The formation of the dichloro compound (160) was explained in

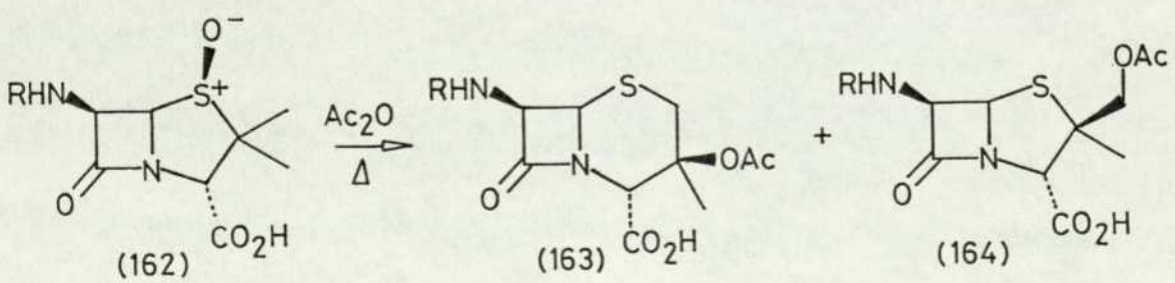


(159) (161) (160)

terms of additional benzylic stabilisation of the initially formed cation (161). However, treatment of (159) with acetic anhydride gave a complex mixture, suggesting that the product (160) may not be the result of a genuine, additive Pummerer reaction.

Penicillins and Cephalosporins

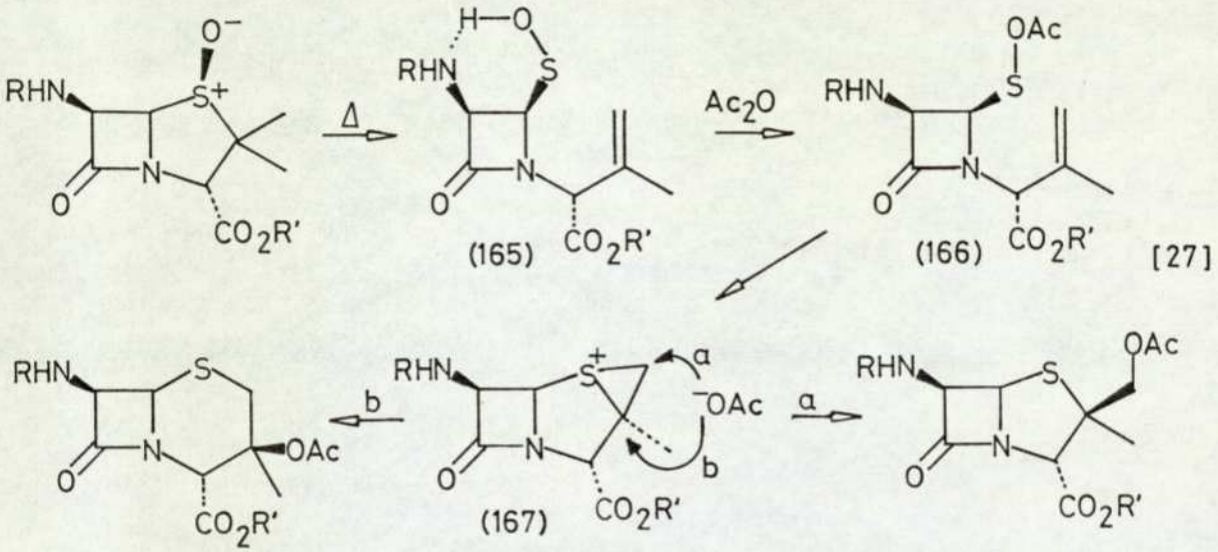
In 1963 Morin and co-workers reported that penicillin S-oxide (162), on treatment with hot acetic anhydride gave the cephalosporin derivative (163) together with the acetoxy-



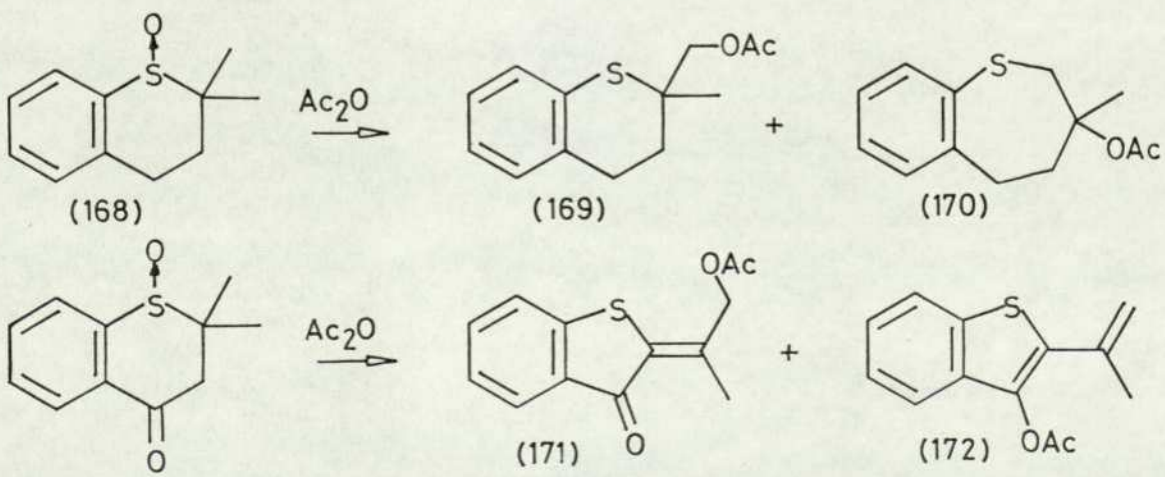
(162) (163) (164)

methyl penam (164). The importance of this transformation

cannot be overstated since it provides an entry into the clinically valuable, but costly, cephalosporins from the relatively cheap penicillins. Consequently the reaction has been studied in great detail and many excellent reviews have been published.[83] The rearrangement, although formally related to the Pummerer proceeds via a distinctly different path (Eqn. 27). Reagents such as acetic anhydride trap the

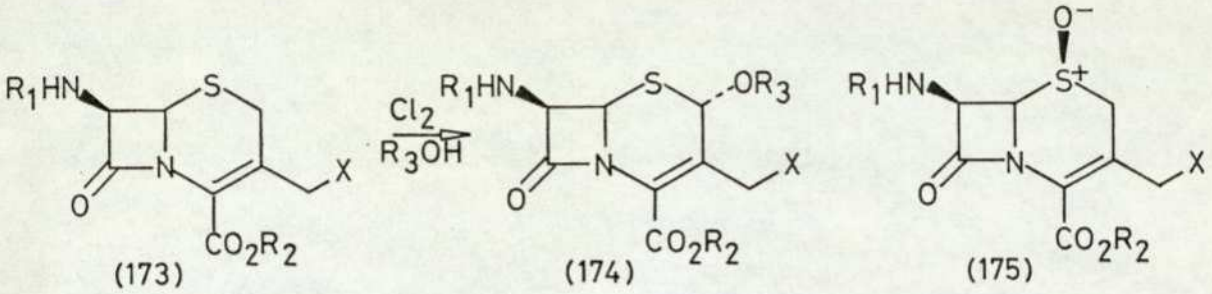


thermally generated sulphenic acid (165) as the mixed anhydride (166). This collapses to the products via the sulphonium ion (167). This type of rearrangement is a common feature of sulphoxides possessing no α-hydrogens. For example, the dimethyl thiachroman S-oxide (168) gave the acetoxymethyl derivative (169), together with the ring expanded product



(170).[84] However, introduction of a carbonyl group β to the sulphoxide completely diverted the reaction to the ring contracted compounds (171) and (172).

The normal Pummerer reaction has also found application, particularly as the means of introducing substituents in the C(2) position of cephalosporins. Thus, chlorination of the cephems (173), in the presence of an alcohol gave the 2-alkoxy



derivatives (174).[85] Treatment of the sulphoxide (175) with acetic anhydride provided the usual rearrangement product (174, R_3 = Ac). A similar result was obtained with alkyl chloroformates.[86]

In conclusion, the Pummerer rearrangement of sulphonium salts, apart from the intrinsic mechanistic interest, has proved to be a versatile, synthetically useful reaction.

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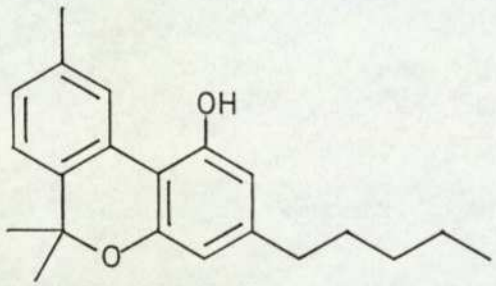
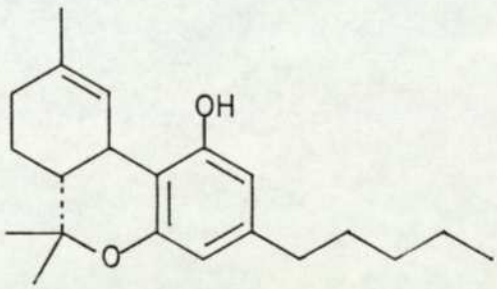
DISCUSSION AND RESULTS

INTRODUCTION

The rich folklore associated with various preparations of Cannabis sativa has attracted the attention of chemists for over 150 years. However, the non-alkaloid nature of the active principle presented the 19th century investigators attempting its isolation with insurmountable problems. Even in the 1930's the inactive cannabinol (1) was the only component available for analysis. The degradative studies of Cahn[1] established its structure and paved the way for the groups of Adams[2] and Todd[3] whose work still forms the backbone of much cannabinoid research. The advent of modern chromatographic and spectroscopic techniques led finally, in 1964, to the isolation and identification of tetrahydrocannabinol (THC) (2) as the active principle.[4]



(1)

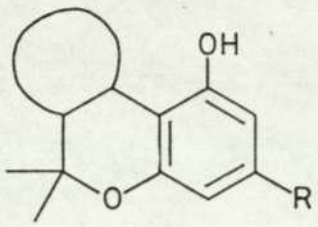


(2)

A considerable body of information embracing the chemistry, pharmacology, metabolism and clinical effects of THC has been gathered in the following decade[5] and the output has remained impressive. A review[6] appearing in 1976 and covering a period of about one year contained over 400 references!

The wide-ranging therapeutic potential of THC[7] has

stimulated great efforts in the preparation and testing of analogs.[8,9] Since the dimethyl benzochroman system with a free phenolic group (3) appears to be the essential structural feature of all active compounds, 5-substituted resorcinols gained important status as the required starting



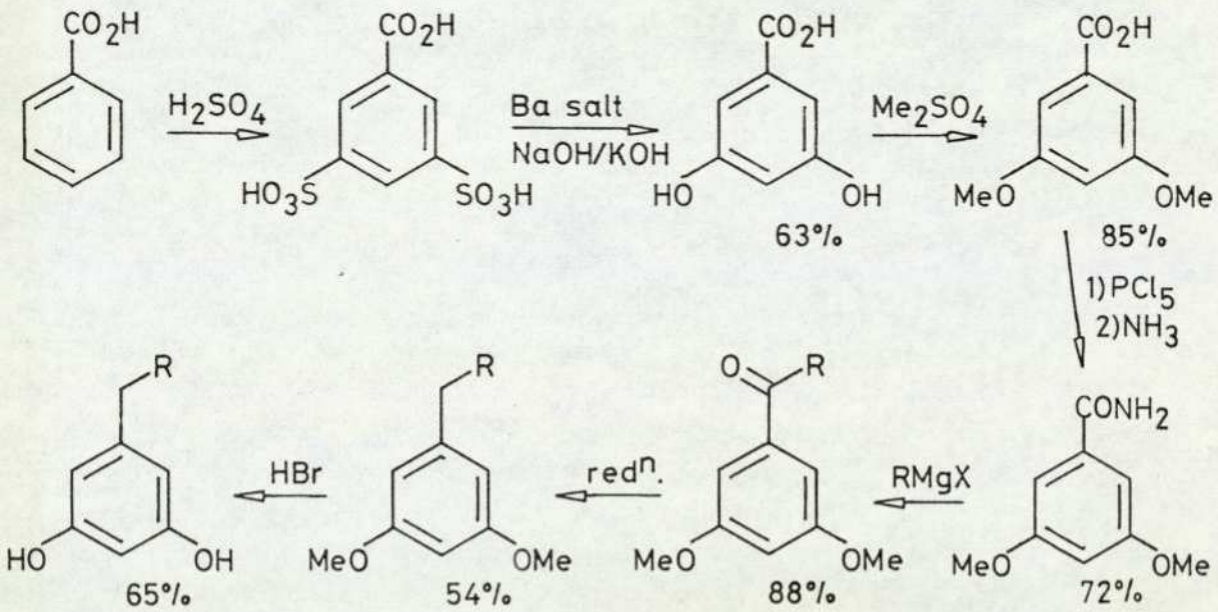
(3)

materials for their synthesis.[10] Such resorcinols are neither cheap (if commercially available) nor readily prepared. For example, olivetol, used to synthesise THC itself,[11] currently (1978) retails at £7.20 per gram.

The aim of the work presented on the following pages was to devise a general and efficient route to these rare, albeit simple, compounds.

CHAPTER 1

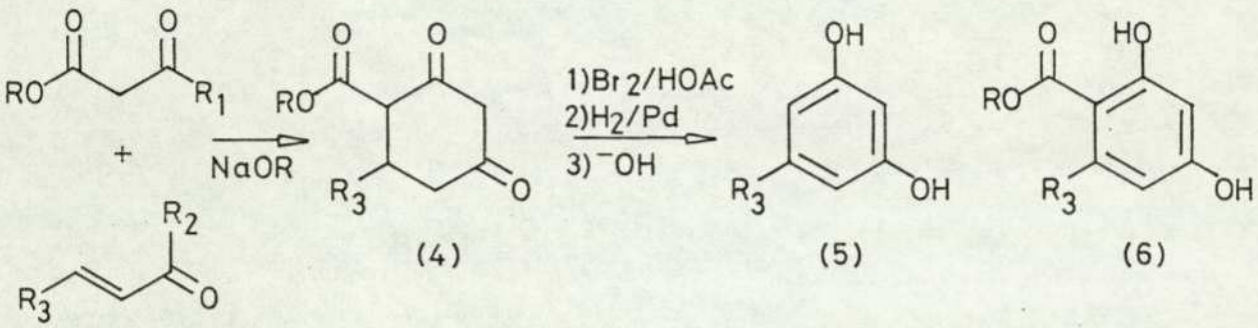
The importance of olivetol and its homologs in the cannabinoid field has meant that most of the published syntheses of 5-substituted resorcinols aimed at the alkyl derivatives. The two routes that gained greatest attention involve elaboration of 3,5-dimethoxybenzoic acid, and its derivatives, and total synthesis from alicyclic precursors. The original method described by Sutter[12] has been adopted by Adams[13] and modified as newer reagents became available.[14] Most of the modern syntheses use the expensive 3,5-dimethoxy



acid as the starting material, but even so the best procedure[14a] requires three steps and can only provide n-alkyl compounds. The usefulness of some of these amendments[14b,d] must be questioned. One can hardly describe a six-step synthesis as an improvement.[14b] The main disadvantages of this type of approach, apart from the rarity of the starting material, are non-generality and the necessity

for eventual demethylation. The yields for the final stage, if quoted, are seldom spectacular.

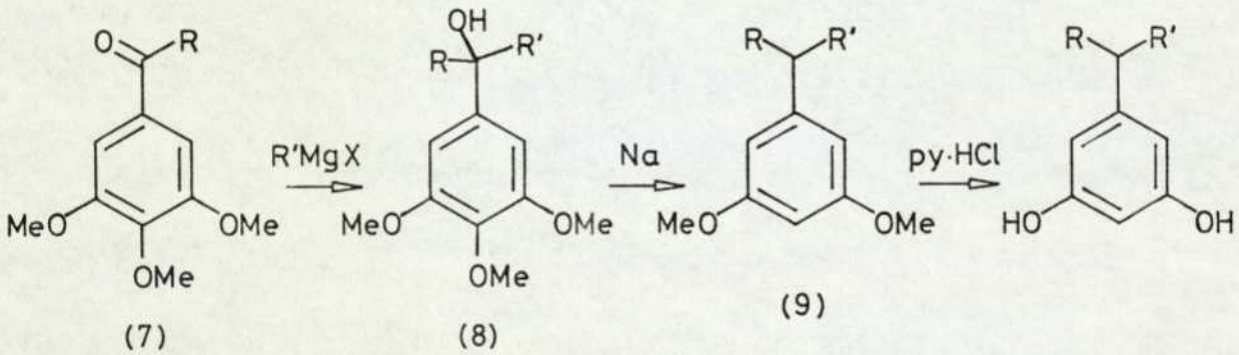
The problem of versatility was partially overcome by the total synthesis. Anker and Cook[15] used acetoacetate and



α,β-unsaturated esters (R_1 = Me, R_2 = OR) to obtain the cyclohexanedione (4) which was converted in three steps to the resorcinol (5) in 25% overall yield. The reaction has been modified since, and the yields, for n-alkyl derivatives, have doubled.[16] Condensation of malonate and an enone (R_1 = OR, R_2 = Me) enabled Sutter[17] to prepare 5-phenyl resorcinol (R_3 = Ph). This alternative was taken-up by the Hoffmann-La Roche group[18] for the synthesis of ^{14}C-labelled olivetol. The most recent modification from the same laboratories utilises bromine in refluxing DMF to effect the transformation (4) → (5) in one-pot.[19] The experimental details are extraordinarily confused, however, listing absurd physical data (e.g. olivetol was analysed as $C_{15}H_{22}O_4$! and showed ν_{max} 1790 and 1710 cm^{-1}?!). From the additional information in a footnote it would seem that the benzoate (6) was the initial product. The obvious disadvantage of these methods is the, rather vigorous, oxidation step which may affect substituents more elaborate than a simple alkyl residue.

This was clearly illustrated by an Australian group[20] attempting to synthesise naturally occurring resorcinols with unsaturated side-chains in the 5-position. None of the reagents tried, such as bromine,[15,19] cupric bromide,[16] or mercuric acetate[18] gave the required aromatic compounds. Another drawback inherent in this approach is of steric origin. Yields are significantly lower with sec-alkyl substituents and no reaction was observed with tert-alkyl compounds.[16]

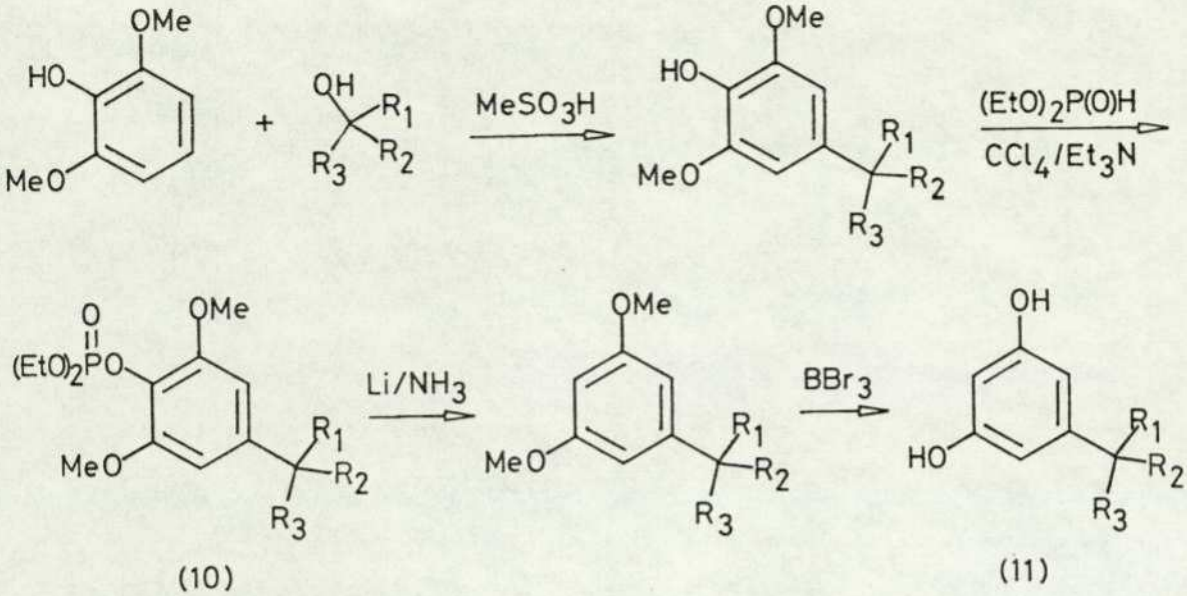
An interesting synthesis based on a reaction discovered by Asahina[21] involves the dissolving metal reduction of the carbinols (8).[22] Although the starting aldehyde (7, R = H) and the ketone (7, R = Me) are less expensive than the



(7) (8) (9)

3,5-dimethoxy compounds the key step is erratic and results in poor quality product (9).

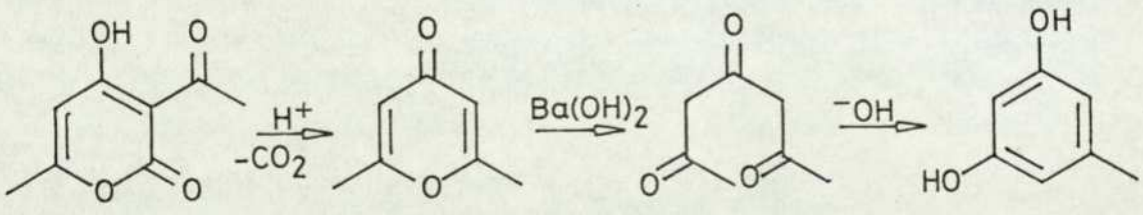
A related method designed specifically for the preparation of 5-tert-alkyl resorcinols has been described recently.[23] Although the reduction of the phosphate (10) and subsequent demethylation were somewhat unpredictable this would appear to be the method of choice for the synthesis of compounds such as (11).



(10) (11)

Alkylation of Dehydroacetic Acid

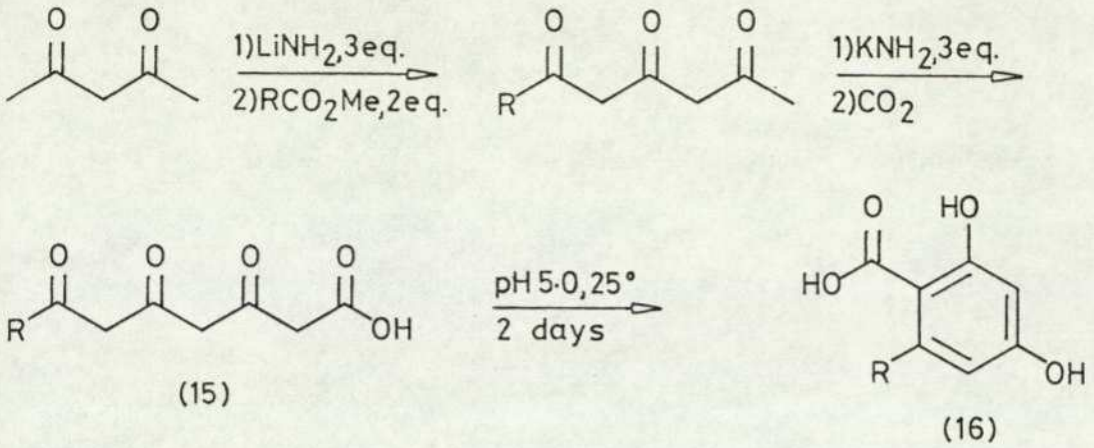
To begin with the feasibility of a biomimetic-type synthesis was explored. Although Collie's original hypothesis of the "multiple ketene group"[24] as a precursor of aromatic phenolic compounds was ignored for half a century, its resurrection as Birch's "acetate hypothesis"[25] led to numerous, biogenetically modelled, syntheses of natural products.[26] Collie was able to isolate a small amount of orcinol from the reaction of the triketone (14), itself obtained from



(12) (13) (14)

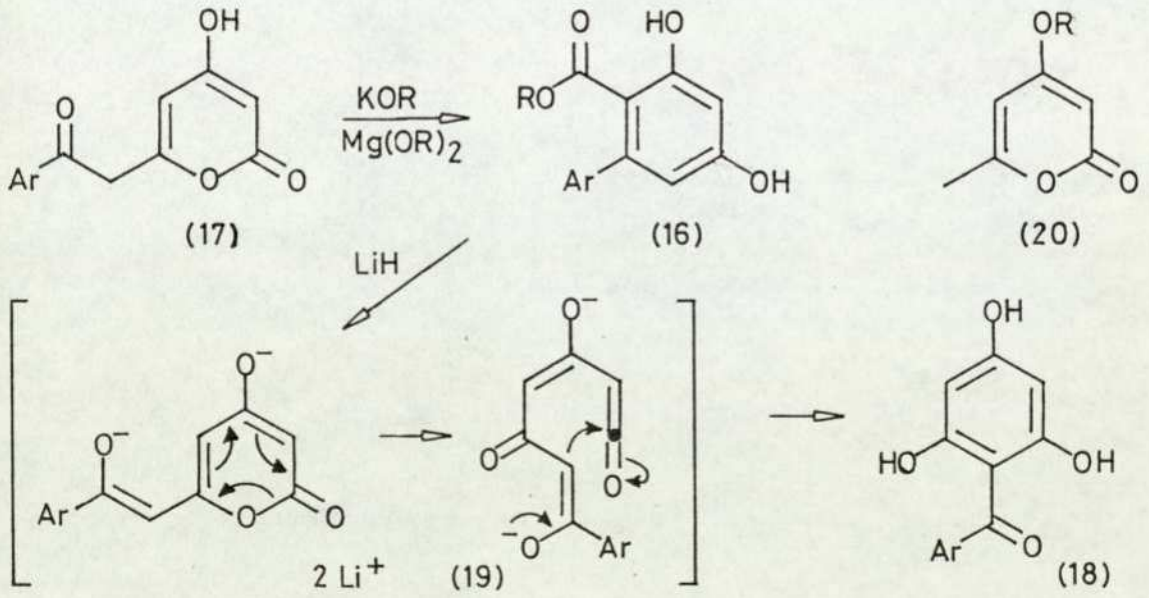
the hydrolysis of 2,6-dimethyl-4-pyrone (13). However, the triketo acids (15), possessing the additional acetate unit, cyclise in virtually physiological conditions to give the

resorcylic acids (16) in high yields.[27] The practicality



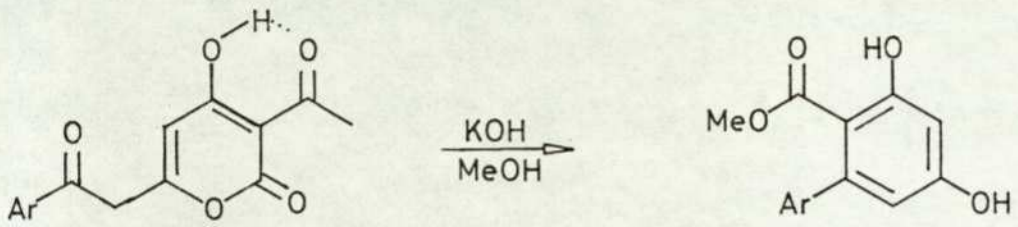
of this reaction is unfortunately limited by the inefficient synthesis of the precursors (15). Harris and his group have developed, and made extensive use of, polyanion chemistry in order to gain access to these, and higher, polyketides.[27,28]

Another source of the triketo acids, described by the same group, are the pyrones (17). On treatment with nucleophilic bases these masked polyketides are converted to the



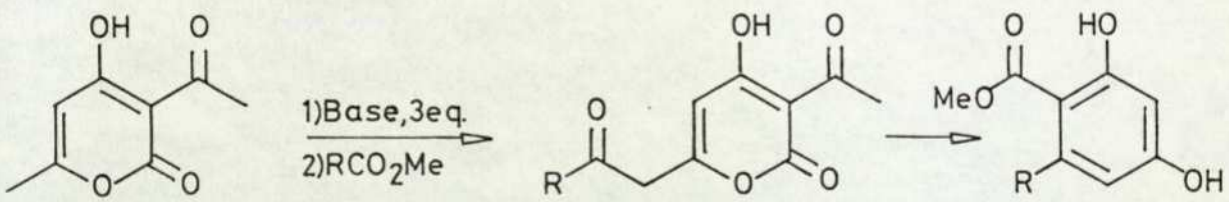
resorcylic acids (16) (aldol products). Non-nucleophilic bases give the acyl phloroglucinols (18) (Claisen products)

via the postulated ketene intermediates (19).[29] The pyrones (17) were obtained by acylation of the dianion of triacetic lactone (20, R = H). Unfortunately only aromatic esters could be used and the yields were modest.[30] However, Harris also found that the trianion of dehydroacetic acid (12) could be alkylated and acylated in good yields at the 6-Me position.[31] Furthermore, the pyrones (21) could also be converted to the



(21) (16)

resorcylic esters (16) with concomitant loss of the acetyl group.[29] Since the acylation of the trianion with aliphatic esters was not described attention was focussed on this very reaction (Scheme 1).

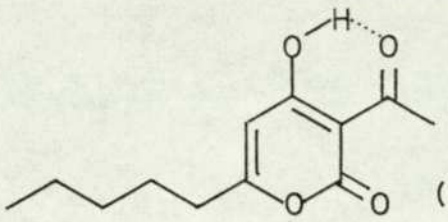


(12)

Scheme 1

In order to gain experience alkylation of dehydroacetic acid was attempted first. Generation of the trianion with 30% excess of sodamide in liquid ammonia proceeded smoothly, and addition of n-butyl bromide gave mainly the expected pyrone (22). The site of alkylation was easily ascertained by comparison of the n.m.r. spectrum of (22) with that of dehydroacetic acid (12). In the starting

material the acetyl Me signal occurs at δ2.68 and the 6-Me appears at δ2.30. This assignment can be made on the basis of observable allylic coupling of the up-field methyl to the vinylic proton. In the product the vinyl-methyl was replaced by a broad methylene triplet at δ2.50. Treatment of (22) with concentrated potassium hydroxide failed, as expected,

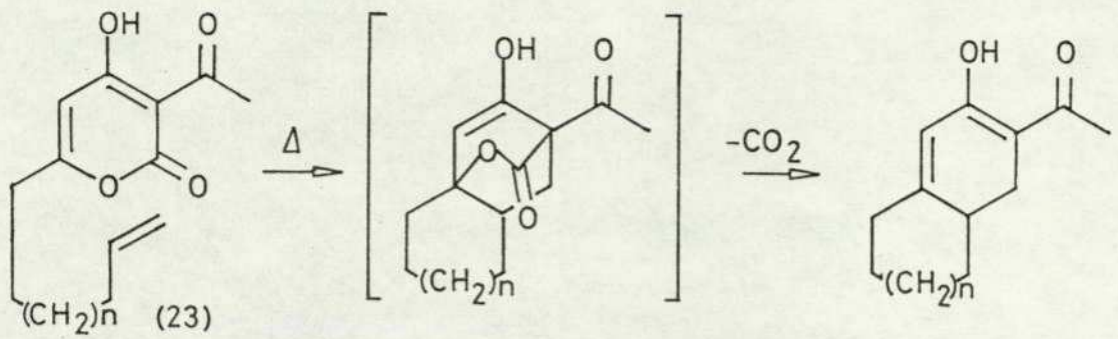


(22)

to produce any olivetol, resulting instead in extensive decomposition.

Encouraged by the successful alkylation, the acylation of the trianion with methyl caproate was attempted. The results were uniformly disappointing, under a variety of conditions, dehydroacetic acid being recovered. Presumably the strongly basic trianion enolised the ester. The proton transfer reaction appears to be the fastest process even with lithium bases. Attempted acylation of triacetic lactone methyl ether (20, R = Me) gave a complex mixture which was not analysed further.

Since the alkylation appeared to work reasonably well another potential application was tried (Scheme 2). Simple 2-pyrones are known to react with dienophiles[32] although no such reactions have been reported for dehydroacetic acid. Alkylation of (12) with an olefinic halide offered an opportunity for investigating the possibility of an intramolecular cycloaddition. Reaction of the trianion with



Scheme 2

pentenyl bromide (n = 2) gave the expected pyrone (23) (n = 2) in about 40% yield together with some dialkylated material. Thermolysis of the crude product overnight at 160° resulted in decomposition. The n.m.r. of the mixture showed, however, the characteristic pattern of a terminal olefin indicating that no cycloaddition occurred. Also, the mass spectrum of (23) did not show a significant peak corresponding to M^+-44. The base peak was m/e 43 and the main fragmentation appeared to be cleavage of the alkyl chain, followed by loss of Me· to give a relatively abundant ion at m/e 153. This ion suffers two successive eliminations of 42 mass units to give peaks at m/e 111 and m/e 69 (Fig. 1). Abundant meta-stable

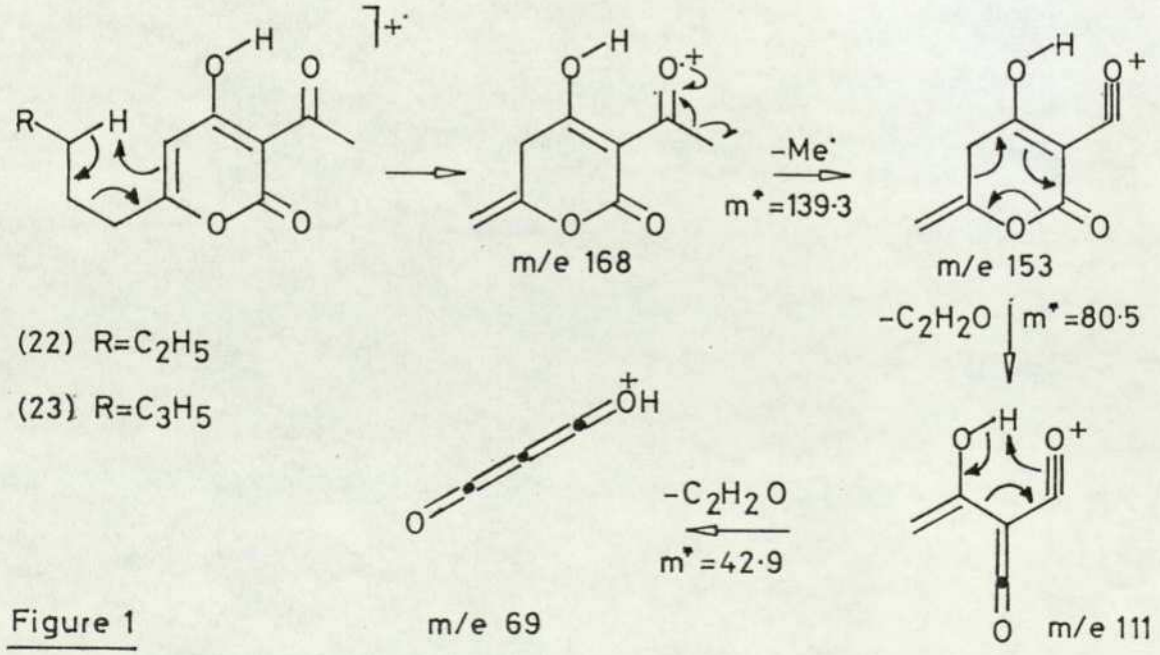
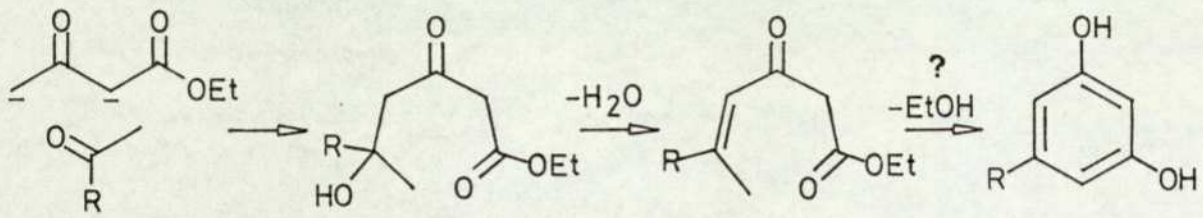


Figure 1

ions confirmed these transitions. Furthermore, the mass spectrum of (22) showed virtually an identical fragmentation pattern.

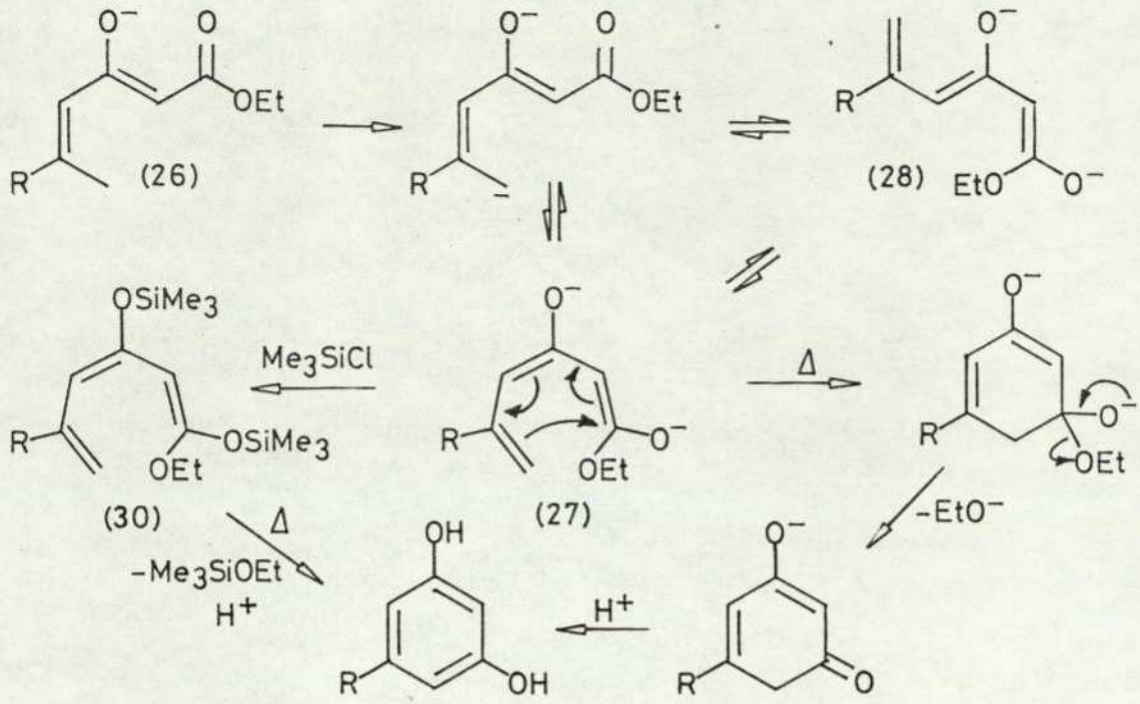
Synthesis of ethyl 5-phenyl-3-oxo-hex-4-enoate (32)

A different strategy, born out of the experience gained in the polyanion field, was next devised (Scheme 3).



Scheme 3

The carbon atoms of a potential 5-substituted resorcinol can be easily derived from readily available starting materials. Condensation of the dianion of ethyl acetoacetate with a methyl ketone would be expected to give the aldol (24).[33] Dehydration should give the olefin (25) whose geometry would be governed by the bulky group R providing mainly the E-isomer. The unknown factor in the proposed scheme was the tantalisingly simple elimination of ethanol with concomitant aromatisation. It was hoped that this could be achieved via the dianion of (25) (Scheme 4). One of the structures of such a species could be represented as (27). This is a reasonable assumption if we consider the initially formed monoanion (26) as a vinylogous equivalent of an α,β-unsaturated ester. The deconjugation of such esters[34] and acids[35] by strong bases has been found to occur readily.



Scheme 4

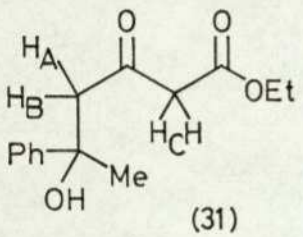
Assuming further that (27) proved a significant contributor, and that the necessary Z geometry about the "central" double bond could be achieved, the dianion could undergo an electrocyclic reaction followed by the expulsion of ethoxide to give the more stable resorcinate (29). The geometry factor seemed the most problematic, the E "central" double bond of (28) being intuitively preferred. Nevertheless if some equilibration between (27) and (28) were to occur then the reaction could proceed in the desired direction.

Alternatively the dianion could perhaps be trapped as the di-silyl enol ether (30) which could have the correct geometry by virtue of the bulky trimethylsilyl group. Again cyclisation, followed by loss of trimethylsilyl ethyl ether should give the aromatic compound. There is good evidence for the formation of reactive silyl ketene acetals from

ester enolates,[36] and even ketene bis-silyl acetals from the dianions of carboxylic acids can be prepared.[37]

The dianion of ethyl acetoacetate was generated using the mixed base procedure developed by Weiler.[33] This simply involves addition of n-butyl-lithium to the sodium enolate of the keto ester. The great advantage of this method is that the only by-products are hydrogen and butane.

Reaction of the dianion with acetophenone gave the expected aldol (31) in over 80% yield. The salient features



(31)

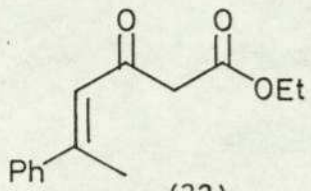
δ2.96	ABq, J = 16 Hz (H_A,H_B)	1.52 s (Me)
3.24		7.2-7.5 m (Ph)
3.35	s ($2H_C$)	

Figure 2

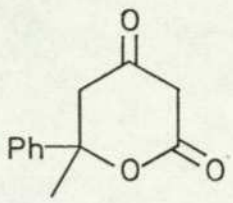
of the n.m.r. spectrum are gathered in Figure 2. The α-methylene protons were found to be exchangeable in deuterium oxide. The aldol could be obtained in very pure state since the unreacted starting materials were easily removed in vacuo. Having successfully assembled the six carbon fragment the proposed dehydration was undertaken. This proved rather more awkward than anticipated.

Treatment of (31) with tosic acid in benzene gave mainly a polar, crystalline compound, although some olefin (32), whose identity was established subsequently, was also formed. The nature of the major product was quickly established from the n.m.r. The ethoxy signals were absent, the methyl suffered a down-field shift and the aromatic multiplet became a broad singlet. The α- and γ-methylenes of (31) were

replaced by two superimposed AB quartets. The structure (33) was therefore confidently assigned. The assignment of the AB



(32)



(33)

quartets followed from the results of D_2O exchange when the one, thus attributed, to the 3-position disappeared. Although no enolisation was apparent in solution, the i.r. spectrum of the solid phase showed absorptions at 3180, 1670 and 1620 cm^{-1} highly characteristic of cyclic β-dicarbonyls.[38]

The formation of the lactone (33), although unanticipated, is not surprising. The reaction is thought to proceed through the relatively stable tertiary, benzylic carbonium ion (34) whose collapse leads to the products observed (Fig. 3).

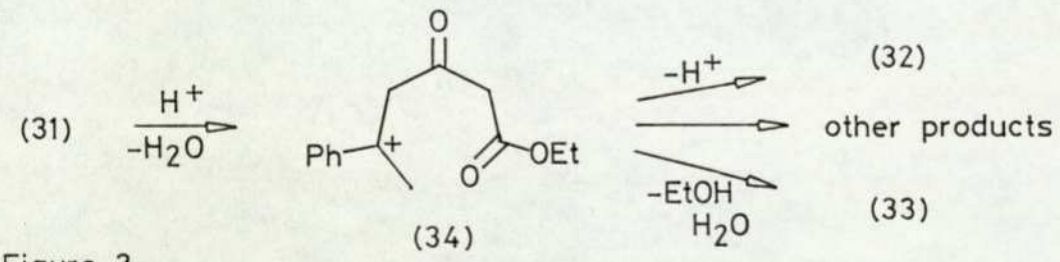


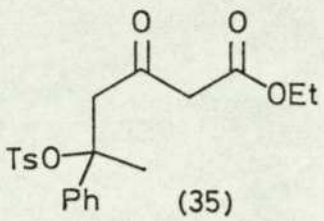
Figure 3

Treatment of the aldol (31) with phosphoryl chloride and with thionyl chloride in pyridine also failed to give appreciable amounts of the olefin. The products from these reactions were not investigated.

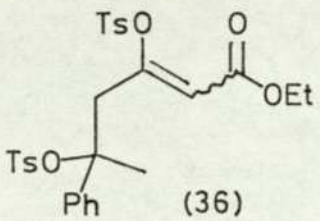
A reportedly mild and efficient method for dehydration of β-hydroxy ketones employs DCC in the presence of cupric salts.[39] This reaction, as followed by t.l.c., proved to be extremely sluggish and even after nine days the greater part

of the starting material remained intact.

Use of tosyl chloride in pyridine also failed to give the olefin. Instead, a less polar major product was observed. Although the n.m.r. of the crude mixture showed incorporation of the p-tolyl moiety the tosylate (35) appeared to be a minor component. The major compound seemed

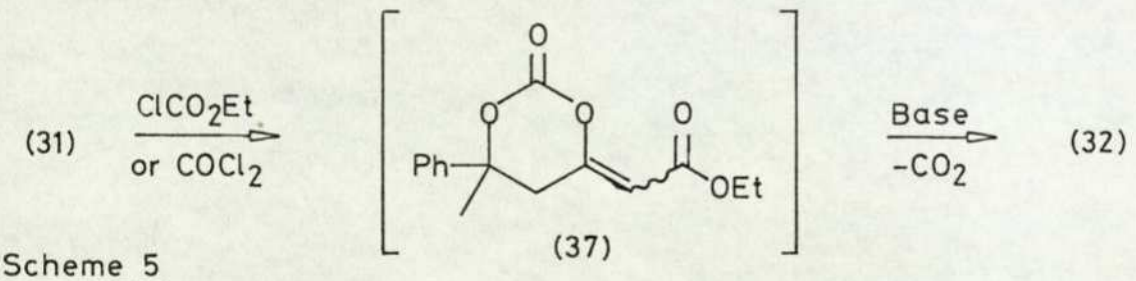


(35)



(36)

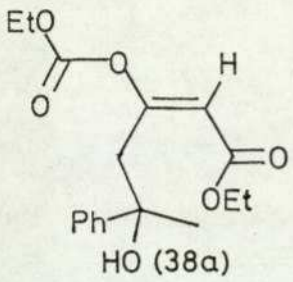
to be the ditosylate (36). Lack of concrete evidence notwithstanding, this curious finding suggested that the dehydration might be effected with intramolecular assistance of the enol (Scheme 5).

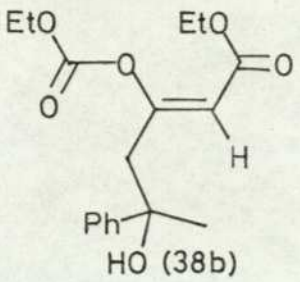


Scheme 5

The cyclic enol carbonate (37) was envisaged as a likely intermediate which should eliminate carbon dioxide to give the required olefin(s). Indeed, the reaction between ethyl chloroformate and the disodio salt of (31) proceeded rapidly, but no gas evolution was detected. The n.m.r. spectrum of a worked-up aliquot revealed incorporation of another ethoxy-group and a one proton singlet at δ5.58. Further, the α-methylene signal of the starting material disappeared and there was still one exchangeable proton. These observations

are consistent with the formation of the enol carbonate (38); the presence of a single vinylic resonance indicating that only one isomer was formed. By comparison with the calculated





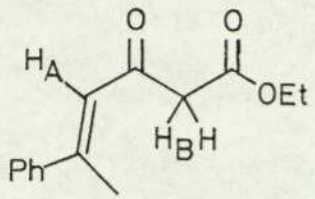
δH	(38a)	(38b)
calc.	5·42	5·19
obs.		5·58

chemical shifts of the olefinic proton the Z configuration (38a) can be tentatively assigned. The reaction failed to proceed any further though. Under forcing conditions a complex mixture resulted.

The analogous reaction of the aldol with phosgene in the presence of pyridine was successful. The n.m.r. spectrum of the crude product showed the three isomeric olefins (32a), (32b) and (32c) to be present in approximately 1:1:1 ratio. Preparative t.l.c. gave mainly the conjugated compounds. The terminal olefin could not be obtained free from the other isomers owing to its instability on silica. Nevertheless the n.m.r. data allowed the unambiguous assignments shown in Figure 4.

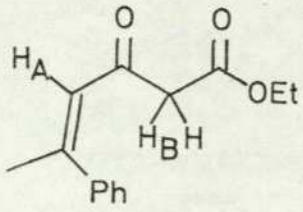
The geometry about the double bond was assigned on the basis of the chemical shifts of the olefinic protons and the vinyl methyls. The methyl singlet in (32a) is 0.4 p.p.m. lower than the methyl in (32b). Furthermore the aromatic resonance in the latter is a complex multiplet as opposed to a broad singlet in the former. Both effects can be ascribed to the deshielding effect of a syn- carbonyl group.

Figure 4



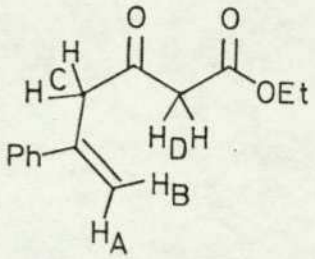
(32a)

δ6.63 1H, bs (H_A)
2.60 3H, s (Me)
3.60 2H, s ($2H_B$)
7.4-7.6 5H, bs (Ph)



(32b)

δ6.27 1H, bs (H_A)
2.22 3H, s (Me)
3.18 2H, s ($2H_B$)
7.2-7.6 5H, m (Ph)

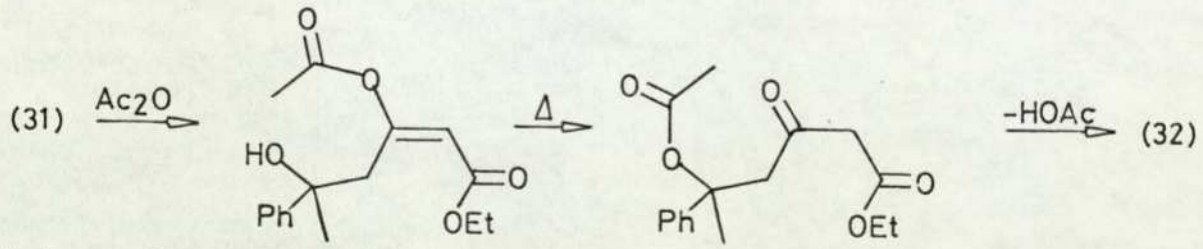


(32c)

δ5.24 1H, bs (H_A)
5.62 1H, bs (H_B)
3.44 2H, s ($2H_C$)
3.73 2H, s ($2H_D$)

Although no evidence was obtained for the intermediacy of (37), the initial reaction of the enol seems most likely. According to this postulate acetylation of the aldol was expected to give the enol acetate (39), which under more forcing conditions could rearrange to (40) (Scheme 6).

The intramolecular acetyl transfer should occur, since the reactivity of the enol acetate would fall somewhere

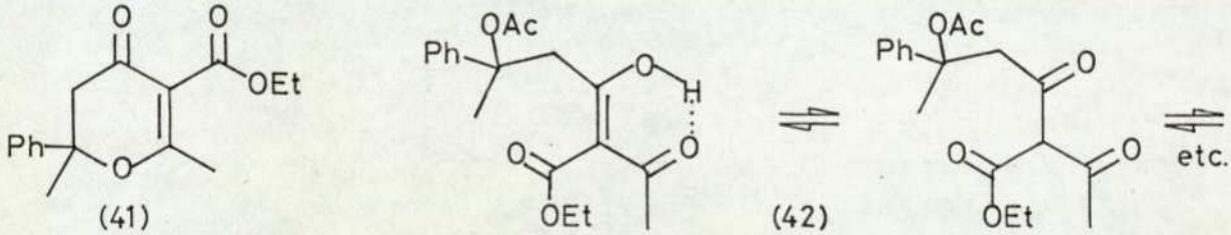


Scheme 6

between that of the inert enol carbonate (38) and that of the unstable enol chloroformate, the presumed initial product in the phosgene reaction. Elimination of acetic acid from the tertiary acetate (40) would complete the sequence. In practice, treatment of the aldol (31) with acetic anhydride in pyridine led directly to the acetate (40) in high yield.

Loss of acetic acid proved equally facile. Stirring the acetate (40) in aqueous, ethanolic sodium hydrogen carbonate resulted in a smooth conversion to the olefin (32a) together with a small amount of (32b).

Since the combined acetylation-decomposition sequence gave the desired olefin in 70% overall yield, it was hoped that a similar result could be achieved more directly. Thus the dianion of ethyl acetoacetate was condensed with acetophenone in the usual way and the reaction quenched with acetic anhydride. Examination of the crude product by t.l.c. suggested that two major compounds have been formed, in addition to the expected acetate (40). The more polar component was readily isolated as a white, crystalline solid and identified as the dihydropyrone (41). The i.r. spectrum showed a strong absorption at 1700 cm^{-1} and a very strong,



broad band at 1670 cm^{-1}, indicative of an unsaturated ester and an unsaturated ketone-enol ether respectively.

The less polar compound could not be satisfactorily separated from the acetate (40). However, treatment of this purified mixture with sodium hydrogen carbonate gave the olefin (32) and the dihydropyrone (41). Since the latter cannot be derived from the acetate (40) the unknown precursor could be the acetyl acetate (42). The n.m.r. spectrum of the starting mixture was consistent with this assignment showing

a low-field signal at δ17.6 and a methyl singlet at δ2.28. The strongly deshielded singlet is good evidence for a firmly hydrogen bonded proton, expected in a structure such as (42).

It would appear therefore that C-acetylation competes successfully with O-acetylation, either initially to give (44), or after the transfer of the acetyl (Fig. 5). The

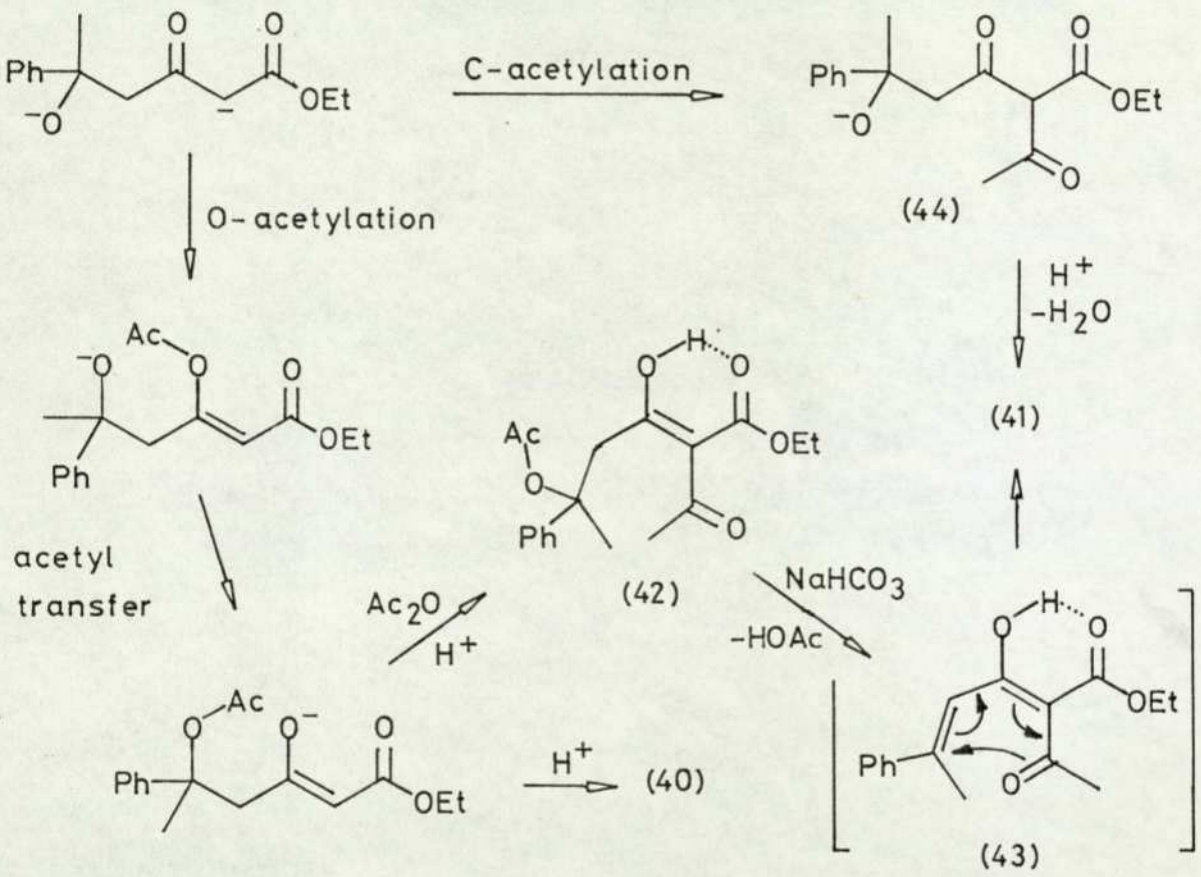
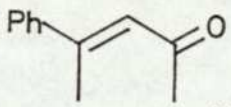


Figure 5

decomposition of (42) occurs presumably via the olefin (43), rather than the alkoxide (44), since the acetate (40) does not revert to the aldol (31) under the same conditions. It is possible that use of just one equivalent acetic anhydride, or acetyl chloride, to quench the original adduct, would give exclusively the acetate (40).

Having obtained a satisfactory method for the synthesis of the starting olefin, the proposed aromatisation (Scheme 4) was put to the test.

Thermolysis of (32a) at 160° for two days resulted in a conversion to a less polar material and considerable tarring. The n.m.r. of the crude products indicated loss of the ethyl group. The α-methylene singlet had also disappeared. However, signals at δ2.52 and δ2.28 indicated that no aromatisation occurred. The product was not identified but it seems likely that it was the ketone (45).

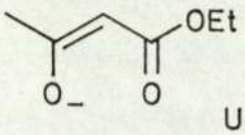


(45)

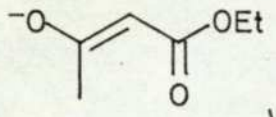
Attempted formation of the dianion with sodium hydride in refluxing benzene was not successful either. The starting olefin was largely recovered. Next, the olefin was added to one equivalent sodium hydride in THF followed by one equivalent n-butyl-lithium. Quenching the deep-orange mixture with dilute hydrochloric acid gave the starting olefin (32a) together with the isomeric (32c) indicating that some deconjugation took place. When an excess of butyl-lithium was used the deconjugation was virtually complete, as evidenced by quenching with D_2O. The major product was the terminal olefin (32c) containing approximately 75% of the label as one of the γ-methylene protons. As expected the α-methylene group was completely exchanged. Disappointingly, the polar residue did not contain any resorcinol. Clearly the dianion, once formed, did not exist in the form which

would permit cyclisation to occur.

In an attempt to influence the geometry of the deconjugated species the reaction was carried out in hexamethylphosphoramide. Enolates of simple β-keto esters are known to exist in the U-shaped conformation in both inert and protic solvents. In very polar aprotic solvents the W-shaped conformation appears to be preferred, minimising dipole-dipole repulsion.[40] Be that as it may, the use of HMPA did

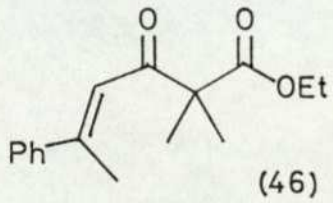


U-shaped

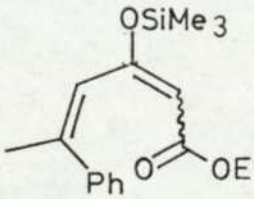


W-shaped

not result in the formation of the resorcinol. A curious result was observed when the reaction was quenched with an excess of methyl iodide. The bis-methylated olefin (46) was isolated in high yield. This may simply reflect failure to



(46)

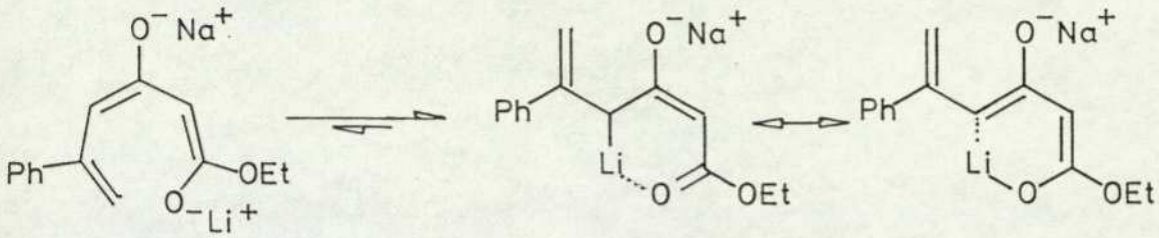


(47)

form the dianion on that occasion. Quenching the dianion solution with trimethylsilyl chloride did not give any aromatic products either. The monosilylated compound (47) could be obtained, as a mixture of isomers, by treating the olefin with trimethylsilyl chloride in the presence of triethylamine. The compound was very unstable and readily reverted to the starting olefin.

This string of failures forced a revision of the original assumption that the dianion would exist as an

equilibrating mixture of the trienes (27) and (28). The aesthetically pleasing resonance forms that can be drawn in



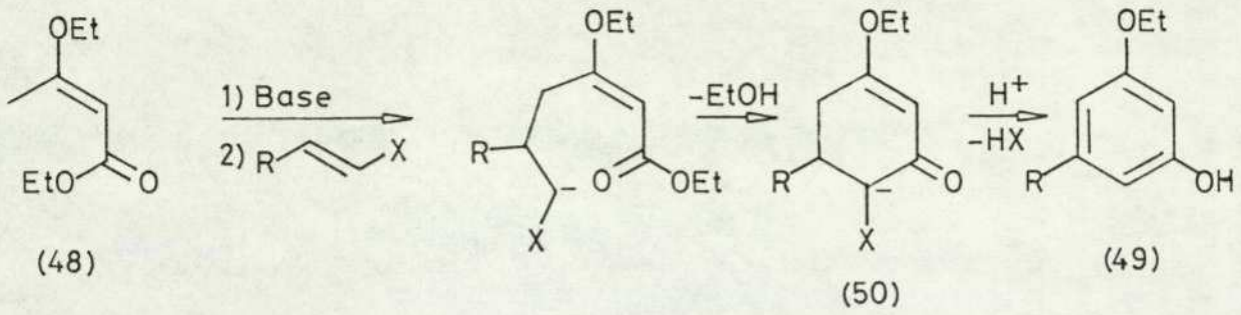
(27) (28)

the case of (28) suggest that this isomer would be overwhelmingly preferred.

It may be possible to convert the olefin (32a) into an enol ether possessing the correct geometry. Such an ether could perhaps be deprotonated with concomitant cyclisation and eventual aromatisation. However, the overall sequence would then become too long and too involved to be of any practical significance. Therefore this Kekuléan approach to the synthesis of resorcinols was abandoned. Nevertheless, the efficient condensation of the dianion of ethyl acetoacetate with the ketone, and the simple method developed for dehydration of the resultant aldol constitute a useful synthesis of the little known systems such as (32).

A modified strategy was devised which would employ the preformed enol ether of ethyl acetoacetate possessing the correct cis-geometry (Scheme 7).

Ethyl 3-ethoxy-crotonate (48) has been shown to form, on exposure to sodium amide, an anion, which reacted readily with aromatic aldehydes. Furthermore, the site of electrophilic attack was exclusively at the γ-position and, importantly, the Z geometry was shown to be maintained

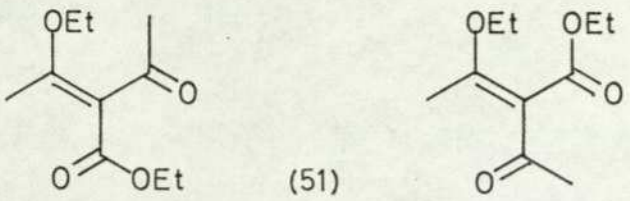


Scheme 7

throughout the reaction.[41] Now, an analogous reaction with a suitable Michael acceptor should give the 5-substituted resorcinol monoethyl ether (49). The function X of the variable component must fulfil several requirements. First, it must be capable of stabilising the developing negative charge; secondly, the anion thus formed should be reactive enough to attack the ester, and lastly elimination of HX should take place readily. Vinyl sulphonium salts (X = $\overset{+}{S}R_2$) seemed to satisfy these requirements to the letter.[42] In a preliminary reaction, however, vinyl phosphonium bromide was used as the Michael acceptor.[43] The anion formation was attempted using lithium di-isopropylamide and the yellow solution quenched with the salt.

Although a transient red colour (indicative of ylid formation?) was observed no product corresponding to (50) (R = H, X = $\overset{+}{P}Ph_3$) could be isolated. The main reaction appeared to be the addition of the amine to the phosphonium salt. The broad peaks in the n.m.r. spectrum of the products also suggested that considerable polymerisation had taken place. Quenching the presumed anion of (48) with acetic anhydride did give rise to two less polar products which

appeared to be the isomeric acyl crotonates (51). This showed that the anion could be formed, but also underlined



(51)

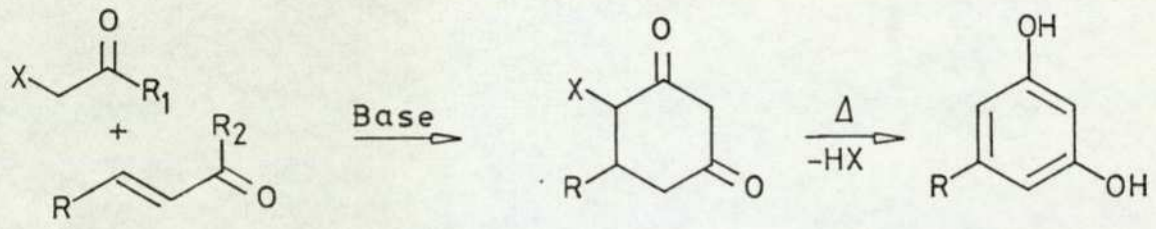
the difficulty of predicting the site of the attack with different electrophiles.[44]

This particular type of reaction was not pursued further since a similar, but much simpler, approach began to bear fruit.

CHAPTER 2

Synthesis of 5-substituted Resorcinols

During the initial experiments with ethyl 3-ethoxy-crotonate it became apparent that the idea of incorporating the oxidant as an activating group could be applied much more simply to the classical synthesis (page 57) (Scheme 8). The nature of the all important function X was determined by the ease with which HX could be eliminated. Probably, the



R_1=Me, R_2=OMe
R_1=OMe, R_2=Me

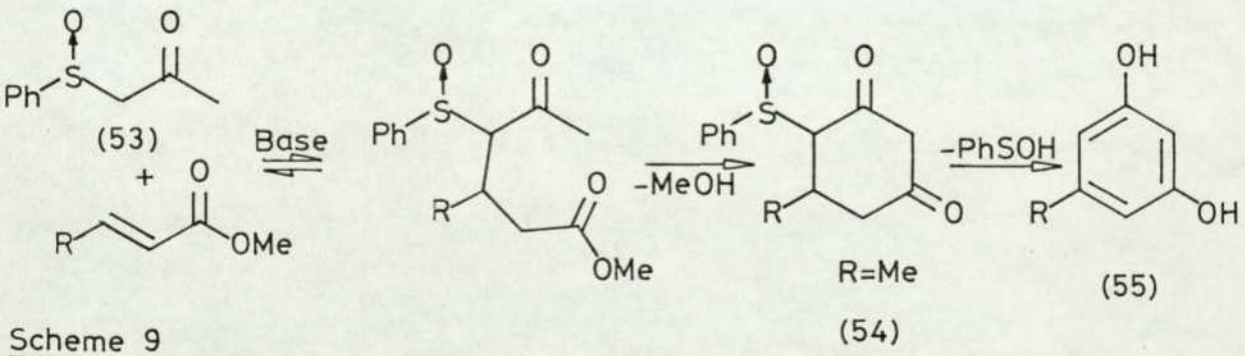
(52)

Scheme 8

two best methods for converting ketones to enones, which utilise the α-substituent, are the thermal eliminations of selenoxides[45] and of sulphoxides.[46] Although the elimination of seleninic acid from a β-keto selenoxide occurs at room temperature, it was of paramount importance that the function X survived until after the cyclohexanedione (52) had formed. This condition is fulfilled by β-keto sulphoxides which are generally stable up to 80°. Furthermore, there is ample precedent that both α-sulphinyl ketones[47] and esters[48] can be alkylated, which implied that the anions should be nucleophilic enough to undergo Michael reactions. It is somewhat surprising therefore to find that this aspect of their

chemistry has been largely ignored. There are apparently only three references dealing with the conjugate additions of α-sulphinyl ketones, and none at all with the analogous reaction of the esters. The first example[49] of a Michael reaction of an α-methylsulphinyl ketone with methyl acrylate appeared in 1968. This prompted a similar disclosure from Russel[50] and from an Indian group.[51] Only Russel isolated the initial adduct. Both the Japanese workers[49] and the Indian team[51] desulphurised their crude products. Neither of these groups reported formation of resorcinols or of cyclic compounds, but none of the cases involved a methyl ketone.

Armed with this meagre knowledge the reaction of phenylsulphinylacetone (PSA) (53) with α,β-unsaturated esters was investigated (Scheme 9). The choice of this substituent X was governed by the known ease with which aryl sulphoxides eliminate sulphenic acid, as compared with the alkyl analogs,[46] and in order to avoid any side-reactions which could occur at the α'-position if an alkylsulphinyl group were used.



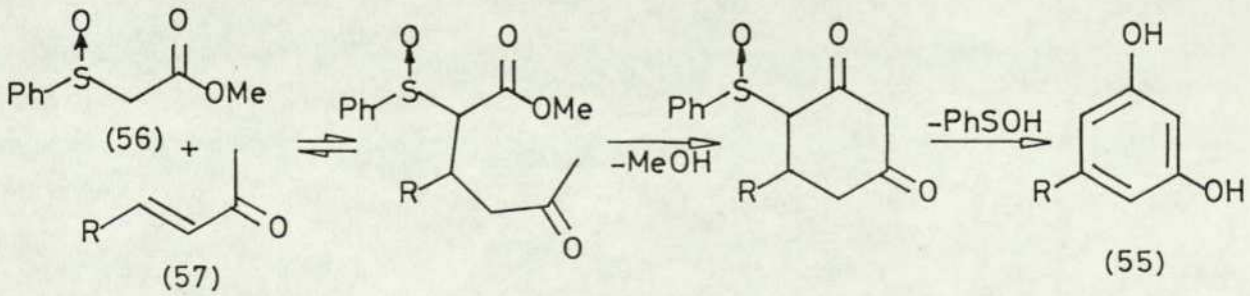
Scheme 9

The keto sulphoxide was readily prepared by oxidation of phenylthioacetone with sodium metaperiodate. Attempted reaction with methyl cinnamate, using sodium methoxide in

methanol, was unsuccessful. However, changing the Michael acceptor to the more reactive methyl crotonate did result in low conversion to orcinol (55, R = Me), under forcing conditions. Although this was encouraging, prolonged heating of solutions containing the PSA anion led to slow decomposition of the reagent. Apparently disproportionation was the main problem.

Since the unsaturated esters remained largely unconsumed the obvious implication was that the initial Michael reaction did not take place at all in the case of cinnamate, and only at a modest rate with crotonate. Another factor is the relatively low reactivity of the PSA anion, since the analogous reactions of ethyl acetoacetate proceed readily.[15,16] The positive aspect of the crotonate experiment was that once the initial equilibrium could be established the reaction would be irreversibly driven to the most stable product, i.e. (55). Whether the elimination of phenylsulphenic acid occurred after the formation of the cyclohexanedione (54) is open to speculation, since under the conditions used it could have happened at any stage prior to cyclisation.

Taking the argument of "relative reactivities" further, interchange of the ester and ketone functionalities was the most logical step (Scheme 10).



Scheme 10

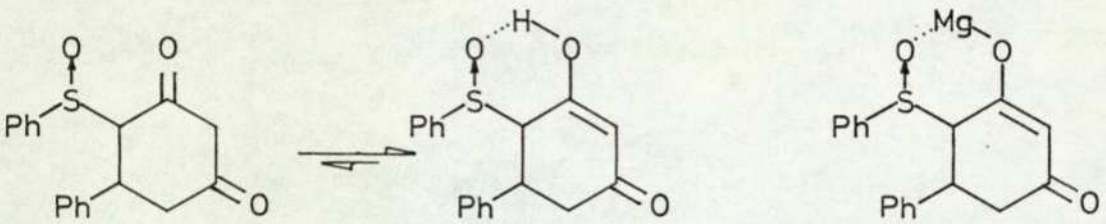
Accordingly methyl (phenylsulphinyl)acetate (56) was prepared and reacted with benzylidene acetone (57, R = Ph) under conditions identical to those used in the cinnamate experiment. The reaction was followed by ^{1}H n.m.r. spectroscopy. The characteristic AB pattern of the olefinic proton was observed to diminish rapidly showing that the reaction did occur in the 1,4-sense. Also, another broad signal began to appear in the same area. The same experiment, when scaled-up, gave directly a 20% yield of pure 5-phenyl resorcinol (55, R = Ph) by extracting the crude mixture with hot water, from which the product crystallised out. This was not a satisfactory procedure since a considerable amount of the resorcinol remained in the residual gum. Diphenyl disulphide, a known disproportionation product of phenylsulphenic acid,[52] was also obtained by steam distillation of the crude products.

Encouraged by this instant success, the reaction was subjected to closer scrutiny.

The sequence of events, as followed by t.l.c. showed a characteristic pattern. Initially a very polar mixture was formed, which gradually gave way to a single, less polar spot and non-polar material. Heating tended to accelerate the disappearance of the polar products. These observations were consistent with the formation of the cyclohexanedione intermediate (58), which would be expected to exist as a mixture of diastereoisomers followed by decomposition to the resorcinol. The ^{1}H n.m.r. spectrum of the crude mixtures also indicated that the intermediate was being formed, since certain signals tended to disappear at the same rate as the

characteristic resorcinol peaks developed. The isolation of the intermediate in appreciable quantities proved somewhat troublesome, however, owing to the continuous decomposition to the resorcinol.

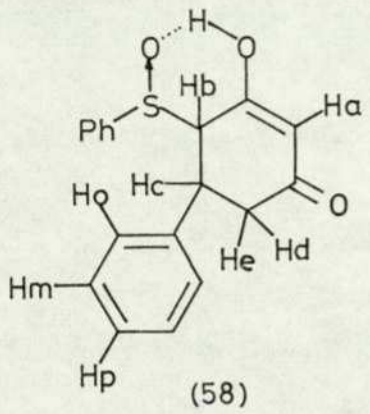
Changing the counter ion from sodium to magnesium appeared to offer several advantages; first, magnesium methoxide is a milder base, and secondly the chelating properties of the metal would be expected to stabilise the intermediate as the enolate (59). The presumed cyclohexane-



(58) (59)

dione was already suspected of preferring the enol form since a singlet at δ5.8 has been observed in the crude mixtures. Indeed, this turned out to be the case. When the reaction was carried out with an excess of magnesium methoxide the polar products were seen to accumulate without appreciable decomposition. The intermediate could be adequately purified by taking advantage of its acidity. Thus, extraction of the ethereal solution of the crude products with saturated aqueous sodium hydrogen carbonate, followed by re-acidification of the alkaline phase and re-extraction into ethyl acetate gave material free from impurities other than the resorcinol and benzene phenylthiosulphinate. The presence of the latter, the initial disproportionation product of phenylsulphenic acid, is the necessary consequence

of the resorcinol formation. Despite these impurities the n.m.r. spectra were clean and yielded useful structural information. The most striking features were: a one-proton double doublet at δ3.20, forming one half of an AB quartet, and a one-proton singlet at δ5.78. Also, one of the phenyl groups was appreciably shielded (Fig. 6).



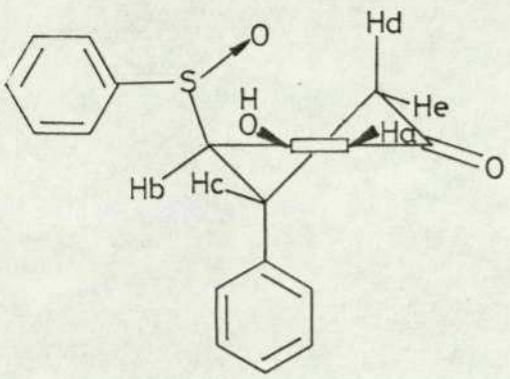
(58)

δ5.78, 1H, s (Ha)
δ3.60, 1H, m (Hb)
δ3.80, 1H, m (Hc)
δ2.64, 1H, bd, J = 18 Hz (He)
δ3.20, 1H, dd, J = 18,6 Hz (Hd)
δ6.80, 2H, m (Ho)
δ7.0-7.2, 3H, m (Hm + Hp)
δ7.2-7.6, 5H, m (Ph)

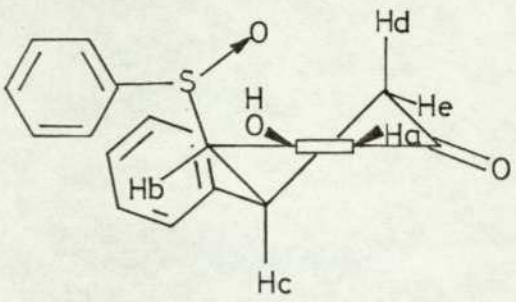
Figure 6

The depicted assignments were confirmed by decoupling experiments. Irradiation of the multiplet at δ3.80 caused the collapse of the double doublet at δ3.20 to a doublet (J 18 Hz) and sharpened the signal at δ2.64. Conversely, irradiation of the double doublet sharpened the multiplet at δ3.80 and collapsed the doublet at δ2.64, but had little effect on the signal at δ3.60. The unusually low chemical shift of one of the methylene protons was readily explained by assuming that the phenylsulphinyl group adopts a pseudo-axial orientation, thus strongly deshielding Hd (Fig. 7). The only two possible conformations which fulfill this requirement are (60) and (61), corresponding to the anti- and syn- isomers respectively. The formation of the latter

Figure 7



(60)



(61)

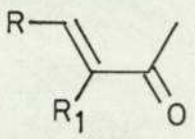
$^{o}_{calc}$	J_{calc} (Hz)	J_{obs} (Hz)	$^{o}_{calc}$	J_{calc} (Hz)
∿80	0-0.5	dc 0-1	∿180	10
∿25	6	ec ∿6	∿80	0-0.5
∿50	4.5	bc 1-2	∿50	4.5

should have been disfavoured on energetic grounds. Nevertheless, the relevant dihedral angles for the two isomers were established, from the examination of molecular models, and the corresponding coupling constants calculated. It can be seen that the calculated, approximate values for the anti-isomer (60) give a much better fit with the observed coupling constants. The shielding experienced by one set of phenyl protons can perhaps be attributed to a quasi-1,3-diaxial interaction with the π-cloud of the enone system. However, at this stage it was not absolutely clear which of the phenyl groups was being affected. Finally, heating the cyclohexanedione intermediate resulted in total disappearance of all the signals discussed above, with concomitant formation of 5-phenyl resorcinol, thus confirming the correctness of the assignments.

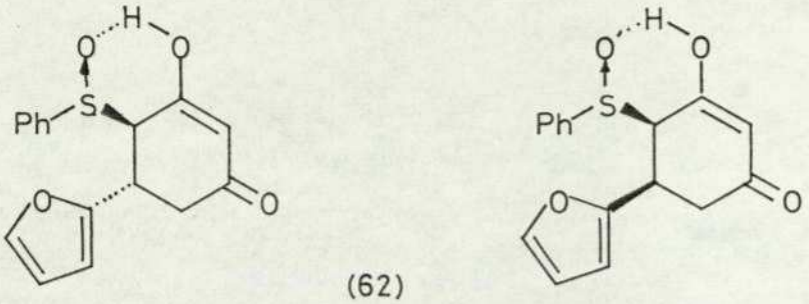
The generality of this novel resorcinol synthesis was investigated using the representative enones shown in Table I. The individual reactions will be dealt with in detail since most of them provided valuable, additional information, pertinent to any future designs. Also at this point, a comment about the yields seems justified. The figures given in Table I correspond to the isolated amounts of pure crystalline compounds but are not representative of mass distribution. For example, the yield of the intermediate (60) as determined from ^{1}H n.m.r. integrals was 57%. The amount of 5-phenyl resorcinol present in the mixture corresponded to 11%. However, the neutral fraction, which contained mainly benzylidene acetone and minor products, when chromatographed furnished 20% of the enone. Taken together these figures correspond to a respectable 85% yield based on unrecovered starting ketone.

Furfurylidene acetone (Entry 3) was chosen as representative of the "sensitive" class of resorcinols which could not be obtained by the classical method, or any of its modifications.[20] The usual conditions gave the unstable cyclohexanedione intermediate (62). Unlike the phenyl case this compound showed two vinylic proton signals at δ5.70 and δ5.80 whose relative intensity tended to vary. Furthermore, only one set of protons attributed to the furyl moiety was significantly shielded, implying that, in this case, both anti- and syn- isomers were formed. The chemical shifts of the methylene and the two methine protons corresponded closely with those observed in the phenyl case, although the

Table I: Reaction of methyl phenylsulphinylacetate (MPSA) with α,β-unsaturated ketones

	Method[f]	% Cyclohexanedione Intermediate[d]	% Resorcinol
1. R = C_6H_5, R_1 = H	A	68	43[a]
2. R = p-C_6H_4-OMe, R_1 = H	A	70[e]	60[a]
3. R = 2-furyl, R_1 = H	A	44	--[b]
	B	--	30[a]
4. R = p-C_6H_4-NO_2, R_1 = H	A	--	26[a]
	B	--	37[a]
5. R = n-C_5H_{11}, R_1 = H	A	58	48[a]
6. R = iso-C_3H_7, R_1 = H	A	41	30[c]
7. R,R_1 = -$[CH_2]_4$-	A	trace[e]	trace[e]

[a] Yields of isolated crystalline compounds, reaction yields were not optimised; [b] $P(OMe)_3$ was used in the thermolysis step; [c] oil; [d] yields calculated from ^1H n.m.r. data; [e] not isolated; [f] method A: $Mg(OMe)_2$/anhydrous MeOH, method B: NaH/THF.



(62)

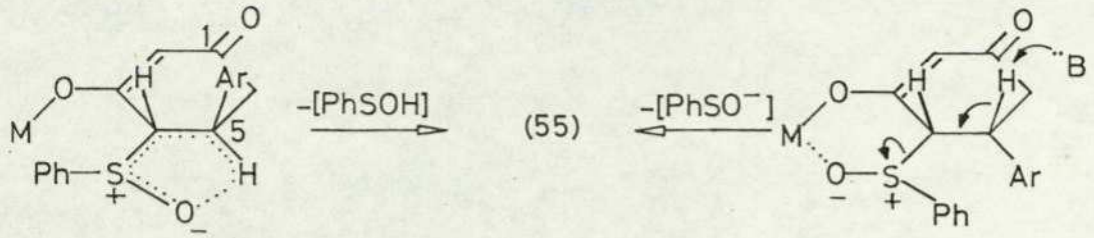
pattern was much more complex, also suggesting the presence of additional diastereoisomers. The alternative explanation of these observations, viz. enolisation in the opposite direction cannot be ruled out, although it is unlikely in view of the subsequent results obtained in the case of olivetol (Entry 5). Again, the relevance of these deductions was confirmed by conversion into 5-(2-furyl)resorcinol. Since the pyrolysis resulted in a product which was not easily purified the use of trimethyl phosphite as the sulphenic acid trap was attempted. This had an even more deleterious effect and gave phosphorus containing products, as evidenced by the doublets (J 12 Hz) at δ3.9. Apparently these compounds were formed after the initial generation of the resorcinol. Powdered calcium carbonate significantly improved the thermolysis step. The use of sodium hydride in THF gave the resorcinol directly and cleanly. The same reaction was also attempted using thallous ethoxide, Triton B and triethylamine. In the former cases the only products were the respective salts of phenylsulphinylacetic acid, and no reaction was observed with the amine. The formation of the thallous salt probably reflects the dubious quality of the reagent. Phenylsulphinylacetic acid was also noticed

when aged sodium hydride was employed. The apparent ease with which MPSA is saponified is doubtless another factor contributing to the successful cyclisation of the initially formed Michael adduct.

The reaction between MPSA and 4-(p-nitrophenyl)-but-3-en-2-one (Entry 4) proceeded rapidly but not too cleanly, possibly due to the sensitivity of the starting ketone. Even when the ketone was added at low temperature (-70°C) there was an immediate formation of intensely coloured (purple-brown) compounds. It is also interesting to note that relatively more of the unidentified products, apparently derived from MPSA, appeared. These unknowns usually formed when basic solutions containing MPSA were refluxed for prolonged periods, and resembled the compounds detected earlier in the reactions of PSA. It is possible, therefore, that a one-electron transfer mechanism may play a significant role in this instance. The formation, dimerisation and other reactions of sulphinyl radicals have been well documented.[53]

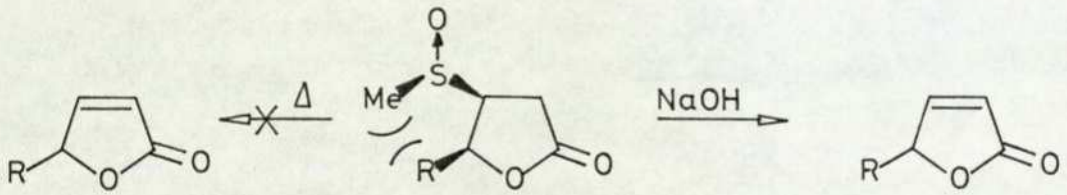
Yet another different feature of this case is that no intermediate could be isolated. One possible rationalisation can be advanced if the mechanism of sulphenic acid elimination is considered. Thermal decomposition of sulphoxides has been shown to proceed through a five-membered, cyclic transition state (Fig. 8).[54] This requires that the sulphinyl group and the proton to be abstracted are syn- to each other. In our case these conditions are ideally fulfilled, since mainly the anti- cyclohexanediones are obtained. Moreover, the benzylic carbon in the 5-position would be expected to

Figure 8



stabilise partial negative charge in the developing transition state, thus greatly lowering the activation energy. This effect would be particularly pronounced with the para-nitro group. At the same time, however, the extra activation provided by the substituent could lead to epimerisation at C(5), and base-catalysed elimination of phenylsulphinate.[55]

A particularly striking example of the latter process was seen by Bartlett in a butenolide synthesis.[56] He found that the crystalline butyrolactone (63) (presumably one of



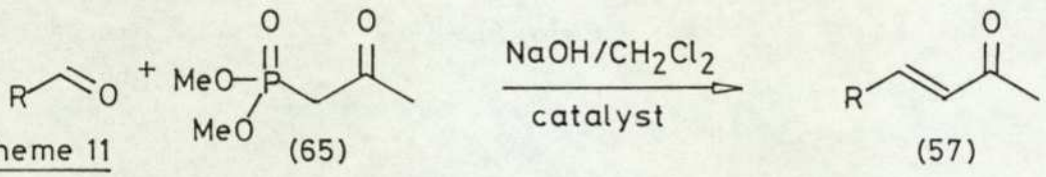
(63) (64)

four diastereoisomeric dl-pairs) was unexpectedly thermally stable. In fact the assigned configuration was deduced from this observation. However, brief treatment with alkali smoothly converted (63) into the butenolide (64).

In the light of these findings the exact sequence of events leading to 5-(p-nitrophenyl)-resorcinol is not at all certain, since the base-catalysed elimination of phenyl-sulphinate could also occur prior to cyclisation.

The preparation of the starting arylidene acetones used thus far was accomplished by conventional means, i.e. condensation of acetone with the appropriate aldehyde in the

presence of aqueous sodium hydroxide. Clearly this reaction could not be applied to aliphatic analogs.[57] A reliable method for the preparation of alkyl enones appeared to be the Wadsworth-Emmons modification of the Wittig reaction.[58] The commercially available dimethyl acetylmethyl phosphonate (65) has been successfully employed by various groups.[59] Traditionally the reactions were performed under anhydrous conditions. The novel technique of "phase-transfer catalysis"[60] appeared to offer a more convenient method of achieving the same results (Scheme 11).

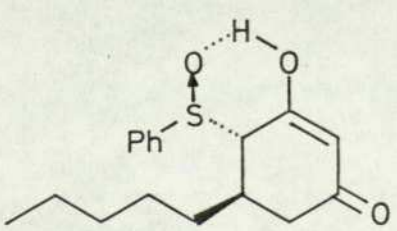


Scheme 11

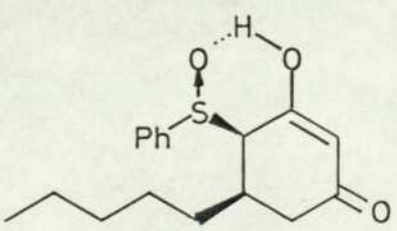
After some experimentation with the available tetra-alkylammonium salts, it was found that excellent yields of enones could be obtained by dropwise addition of stoichiometric amounts of the reagent and the aldehyde, in dichloromethane, to an aqueous solution containing one equivalent of sodium hydroxide and a catalytic amount of tetra-n-butylammonium bromide. In this way non-3-en-2-one (57, R = n-C_5H_{11}) and 5-methyl-hex-3-en-2-one (57, R = iso-C_3H_7) were prepared from caproaldehyde and iso-butyralehyde, in 82% and 74% yields respectively. The ease of work-up and the purity (>90%) of the products make this method particularly attractive. Generally the crude products were used in the next step. The same sequence was to have been applied to the synthesis of 4-(1-adamantyl)-but-3-en-2-one (57, R = 1-adamantyl). However, the laboriously prepared aldehyde

was found to have decomposed after standing overnight in dichloromethane. Apparently decarbonylation of bridgehead aldehydes occurs readily in chlorinated solvents (via a radical mechanism) in the presence of peroxides![61] The instability of the aldehyde is eloquently expressed by the literature descriptions of the compound, ranging from an "unstable oil",[62] through a solid "m.p. 139-141°",[63] to a solid "m.p. 197-197.3°".[61] The latter "later showed erratic melting behaviour". No further attempts to obtain the adamantyl-substituted enone were made since it became apparent that this compound would be very unlikely to add the MPSA anion (page 105).

The reaction of MPSA with non-3-en-2-one proceeded cleanly, though more sluggishly than with arylidene acetones. As expected the intermediate cyclohexanedione was less thermally labile than the analogous aryl substituted compounds, and could be obtained virtually free of olivetol. The purified product consisted of two isomers judging from its t.l.c. and n.m.r. properties, which showed two vinylic signals, and its reduction with phosphorus tribromide,[64] which gave two less polar spots of similar R_f. The two isomers, formed in the ratio 2:1 were assigned structures (66) and (67) respectively on the following evidence. In the n.m.r. spectrum of (67) the <u>exo</u>-methylene group appeared



(66)



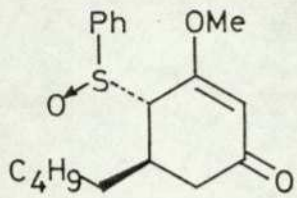
(67)

at δ2.0, whilst in (66) the same protons occurred at δ1.4 as a shoulder of the main envelope. This can be best accommodated by assuming a syn- relationship between the side-chain and the phenylsulphinyl group. In fact the whole of the alkyl residue in (67) was noticeably deshielded relative to (66). Such long range effects have been previously observed, and used diagnostically, in steroidal sulphoxides.[65] Furthermore, the minor product, obtained as a white powder, remained virtually unchanged after one week at room temperature. During the same time, 40% of the major isomer, which was an oil, decomposed to olivetol.

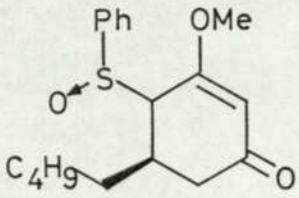
The strict geometric requirements of sulphoxide fragmentation[66] correlate exactly with the relative thermal stabilities of the two products. The anti- isomer possesses the ideal configuration; the syn- isomer could only attain a quasi-planar transition state at the expense of introducing severe strain into the cyclohexane ring. The asymmetry of the sulphoxide group adds another dimension to this picture. The two diastereoisomers in each series should eliminate phenylsulphenic acid at different rates, depending on the gravity of non-bonded interactions in the transition state. The contrast should be more discernible in the inherently crowded syn- series. Since steric factors would presumably play a dominant role in determining the activation energy, one ought to be able to deduce the relative stereochemistry of the four diastereoisomers from their thermal stabilities. Unfortunately the required separation of the syn- and anti- series into their components could not be accomplished

by routine chromatography. The compounds tended to streak reflecting their acidity, and possible tendency to epimerise.

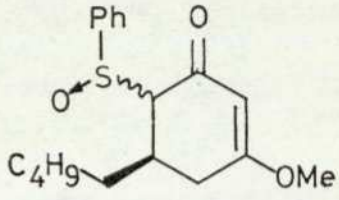
Methylation of the original mixture, however, did give four separable products represented by the structures (68) and (69). The complete n.m.r. data is presented in Table II. The genuine diastereoisomeric nature of the compounds is



(68)



(69)

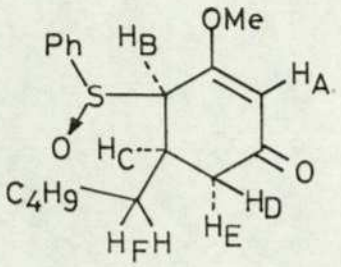


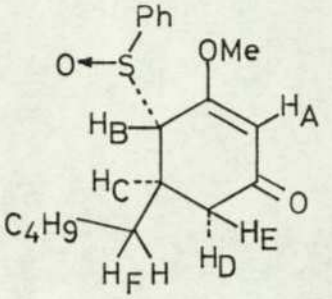
(70)

supported by the large variation in the position of the methoxy singlet and by the chemical shift of the proton α- to the phenylsulphinyl group. The alternative structures (70) cannot simultaneously accommodate both facts. The absence of positional isomers indicates that enolisation of the cyclohexanedione intermediates occurs in one direction only, i.e. towards the sulphoxide. The assignments shown in Table II were deduced as follows. The syn- and anti- configurations were determined using the deshielded exo-methylene criterion. The positions of ring protons followed from the chemical shifts, and their relationship was confirmed by decoupling experiments. In the case of Anti-B for example, irradiation of the multiplet at δ2.75 sharpened the doublet at δ2.28 and collapsed the signal at δ3.26 to a doublet (J 18 Hz).

Irradiation of H_E removed the 18 Hz coupling from the double doublet and vice-versa. Finally, irradiation of the shoulder at δ1.4 sharpened the multiplet due to H_C. The

Table II: ^{1}H N.m.r. data for the methylation products of the cyclohexanediones (66) and (67) (δ values)

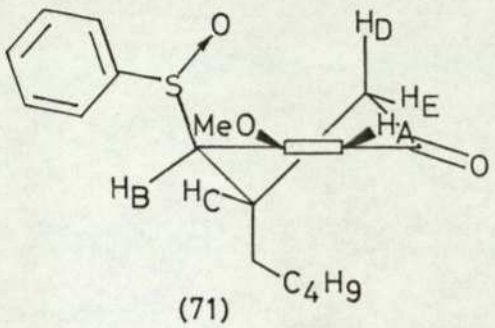




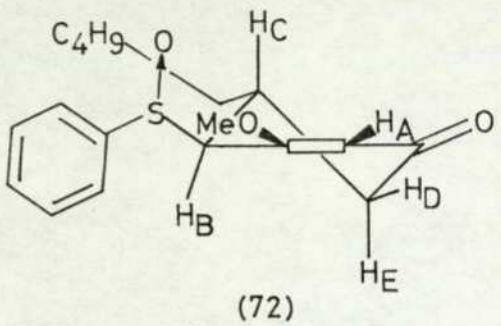
	Syn-A	Syn-B	Anti-A	Anti-B
OMe	3.22 s	3.76 s	3.47 s	3.77 s
H_A	5.60 s	5.50 s	5.45 s	5.45 s
H_B	3.48 bd (J 4 Hz)	3.29 d (J 4 Hz)	3.28 bs	3.24 bs
H_C	2.68 m	2.6-3.2*	2.74 m	2.75 m
H_D	2.78 bd (J 13 Hz)		3.13 dd (J 17,6 Hz)	3.26 dd (J 18,7 Hz)
H_E	2.41 dd (J 13,2 Hz)	2.42 bd (J 14 Hz)	2.34 bd (J 17 Hz)	2.28 bd (J 18 Hz)
$2H_F$	1.80-2.08 m	1.80-2.06 m	shoulder at 1.4	shoulder at 1.4
Ph	7.5 s	7.5 s	7.5-7.7 m	7.5-7.7 m

* Complex pattern

overall pattern displayed by the protons H_B, H_C, H_D and H_E, of the anti- diastereoisomers, was very similar to that noted earlier for the 5-phenyl intermediate. The unusually low chemical shift of H_D again strongly suggests that the preferred conformation in the anti- series is the trans-diaxial one (71), shown here for the enantiomers possessing



(71)

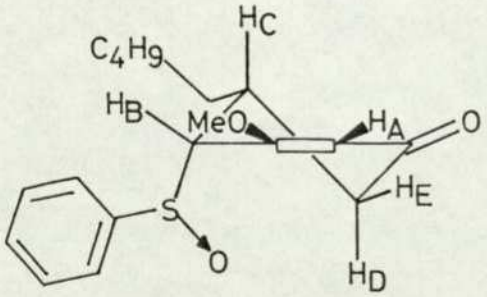


(72)

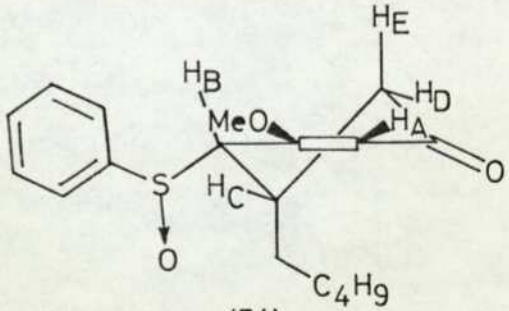
the R configuration at C(5). (For the sake of clarity and consistency this stereochemistry will remain our point of reference although the compounds themselves are, of course, racemic.) The conformation (71) would be also preferred on thermodynamic grounds, relieving the $A^{(1,2)}$ strain[67] present in the trans-diequatorial (72). The significant coupling constant between H_C and H_D is possibly due to the slight puckering of the cyclohexenone ring away from the half-chair conformation. This would have the effect of lessening the 1,3-diaxial interaction between H_D and the phenylsulphinyl substituent and would also result in the narrowing of the dihedral angle between H_C and H_D. By the same token the dihedral angle between H_C and H_E would be increased thus resulting in a very small coupling between these two protons, as is indeed the case.

The differences between Anti-A and Anti-B are essentially

confined to the chemical shifts of the methoxy singlet and the protons constituting the AB quartet. Both of these observations are easily explained in terms of opposite configurations at the chiral sulphur. The discrepancies between the syn- isomers are more striking. In addition to the very large change in the position of the methyl singlet and the appearance of the AB quartet, the chemical shifts of H_A and H_B are significantly different. The values for Syn-B correspond closely with those observed for the anti- isomers, which suggests that the phenylsulphinyl group continues to adopt the pseudo-axial orientation. This demands that the alkyl group be equatorial, and that a large coupling should be seen between H_C and H_D. Although no meaningful decoupling data could be obtained, the complex pattern shown by the two protons in question implies that they are strongly coupled (~10 Hz). Taken together these observations suggest that the preferred conformation of Syn-B is (73).



(73)



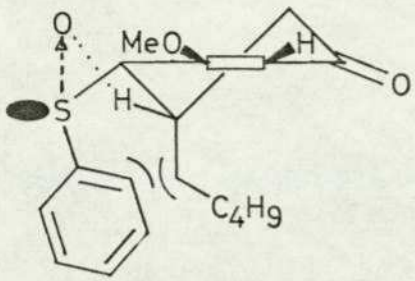
(74)

In Syn-A the observed couplings of protons H_B, H_D and H_E to H_C are small, indicating the absence of any trans-diaxial relationships. Furthermore, the difference in the chemical shifts of H_D and H_E is only about half of that observed in the other diastereoisomers, suggesting that the

influential sulphoxide no longer occupies the pseudo-axial position. Therefore the preferred conformation of Syn-A must be (74). The pseudo-equatorial orientation of the phenylsulphinyl group neatly explains the remaining differences. The deshielding experienced by H_B, now pseudo-axial, finds analogy with the conformationally rigid, α-substituted cyclohexanones and decalones.[68] The unusually high chemical shift of the methoxy singlet is presumably the result of the phenylsulphinyl group being held in the same plane. The reasons why the two syn- diastereoisomers adopt opposite conformations are not immediately obvious. One possible explanation will be offered after, and as a result of, consideration of relative stereochemistries.

As anticipated (page 92), the thermal stabilities of the four isomers varied significantly. Syn-A was a sharp-melting, stable solid, whilst Syn-B, although also a solid, melted over a wide range with extensive decomposition. The two anti- isomers were oils, unstable at room temperature. Unfortunately, no clear-cut difference could be observed in their rates of conversion to olivetol mono-methyl ether. The discussion must be therefore confined to the syn- series.

The thermal stability of Syn-A relative to Syn-B, implies that the former cannot attain the five-membered transition state leading to the elimination of phenylsulphenic acid. Assuming that this is due to steric factors and considering the two possible transition states, (75) and (76), the relative stereochemistry of Syn-A, and therefore of Syn-B, can be established. In (75) there is a severe



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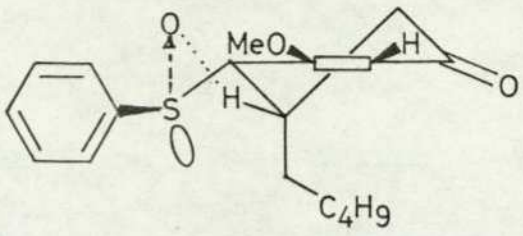


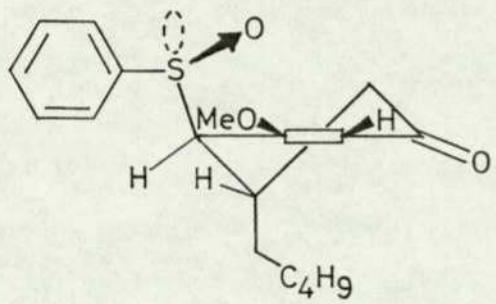
(76)

interaction between the phenyl and the alkyl group. No such hindrance is experienced in (76). Therefore the Syn-A isomer possesses the relative stereochemistry depicted in (75). Consequently, (76) must represent Syn-B, shown here in its "flipped" conformation. Using the R configuration at C(5) as the previously defined point of reference Syn-A can be described as (±) $R_{(S)}$, $R_{(C-4)}$, $R_{(C-5)}$. Applying the same convention, Syn-B now becomes (±) S, R, R.

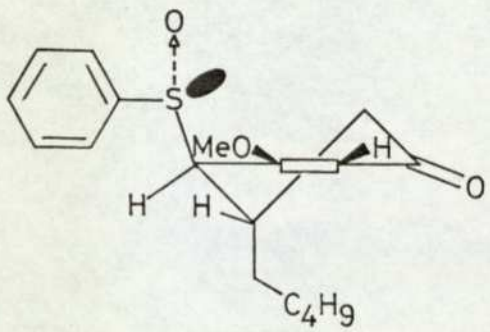
Although an analogous argument could not be applied in the anti- series, the relative stereochemistries could be deduced from the result of an experiment which, fortuitously, went wrong.

In an attempt to obtain more of the syn- isomers the solid fraction of the cyclohexanedione intermediate (67) was methylated with diazomethane. The reaction was carried out in methanol, since the white powder was insoluble in ether. Surprisingly only traces of Syn-B were observed. The main products were Syn-A and Anti-B, formed in an approximately 1:1 ratio. Now, the methanol used was slightly basic, since it was routinely purified by distillation from magnesium.

The weakly alkaline medium apparently epimerised the enolic precursor of Syn-B, so that, upon addition of diazomethane, Anti-B was formed. The syn- to anti- conversion must clearly involve inversion at C(4), but it is extremely unlikely that it would also include inversion at the trigonal sulphur.[69] We can conclude, therefore, that Syn-B and Anti-B possess the same relative configuration at C(5) and at the sulphur. Using our convention, the Anti-B diastereoisomer (77) can be described as (±) SSR and Anti-A (78) as (±) RSR. That leaves the question of why only the enolic precursor of Syn-B epimerised.

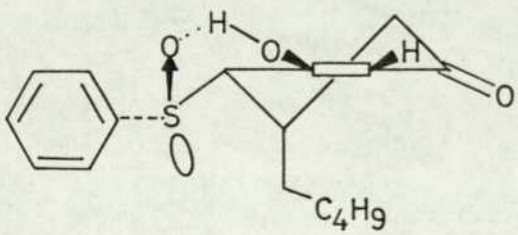


(77)

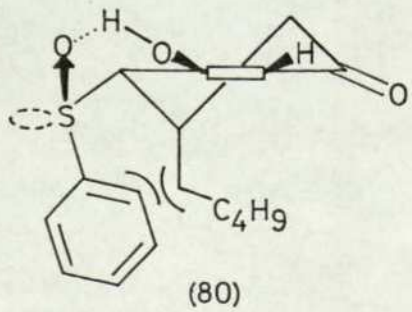


(78)

A plausible rationale can be advanced if the effects of hydrogen bonding, in the two diastereoisomers constituting (67), are taken into account. The two precursors of the syn- enol ethers can be represented as (79) and (80). The



(79)



(80)

conformations shown are entirely reasonable since the n.m.r. spectrum of (67), although ill-defined, resembled quite closely that of Syn-A. It will be seen that the effect of hydrogen bonding in (80) is to bring the phenyl and the alkyl groups closely together thus raising its ground-state energy relative to (79), in which the non-bonded interactions are minimal. In other words, hydrogen bonding will stabilise (79) but not (80). Taking this argument further, one would predict that, of the two diastereoisomers, (80) would be the most likely to undergo epimerisation, or conformational inversion. Now, it will be noted that the relative stereochemistries of (79) and (80) correspond to those of Syn-A and Syn-B respectively. This gratifying correlation adds considerable substance to the *a priori* considerations.

The reason why only the enolic precursor of Syn-B was epimerised is already clear. The "hydrogen-bonding theory" can also explain why Syn-A and Syn-B adopt different conformations, if it is assumed that the Syn-B-type conformation (73) is inherently more stable than (74).[67] The presence of a strong hydrogen bond in (79) prevents inversion of the cyclohexenone ring, and the enol is trapped to give the "kinetic" conformer (74). In the absence of hydrogen bonding, as in (80) the "thermodynamic" conformer (73) is preferred. The barrier to inversion is evidently large.

To complete the account of olivetol synthesis, it should be mentioned that, unlike in the case of enol ethers where Syn-A did not eliminate phenylsulphenic acid, the

entire cis- intermediate (67) decomposed smoothly to olivetol when heated in solution, or upon melting. This requires that (79), as well as (80), should be epimerised. In this case, however, the inversion at C(4) may occur via a series of keto-enol equilibria (Fig. 9). The acidic nature of the cyclo-

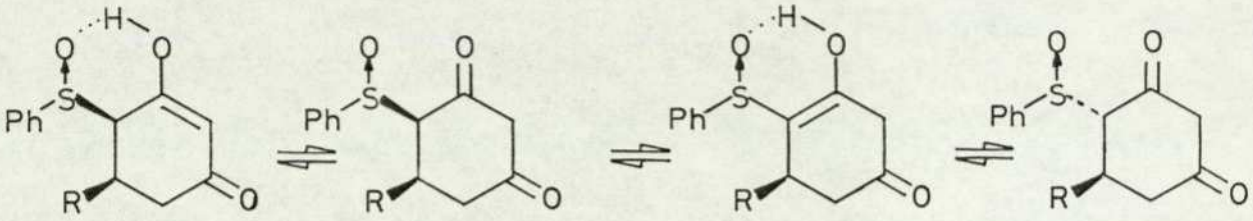
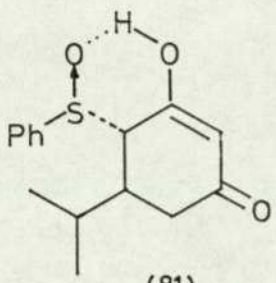


Figure 9

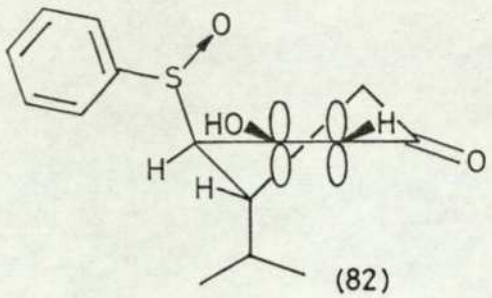
hexandiones has already been noted, so the equilibration could be acid-catalysed. In fact, the vinylic proton in all of the intermediates is readily exchanged, confirming the rapid keto-enol tautomerism. Incidentally, this provides a method for selectively introducing a label in the 2-position of the resorcinol. Heating the deuterated intermediate, from an n.m.r. sample, resulted in labelled olivetol, with virtually quantitative incorporation of the isotope.

The synthesis of 5-iso-propyl resorcinol (Table I, Entry 6) is seen to have been less efficient than that of olivetol. The reaction proceeded at a leisurely pace and was accompanied by formation of non-polar products, apparently derived from self-condensation of the enone. This competing process may be due to the sensitivity of the ketone, but it also underlines the reluctance of the initial Michael step. Nevertheless, the intermediate (81) could be isolated, despite the prolonged reaction times, illustrating the stabilisation provided by the magnesium. As would be

expected, the trans-isomer was formed preferentially, if not exclusively. The characteristic n.m.r. pattern of the C(6) methylene group indicated that the trans-diaxial conformation (82) was adopted. The doublet due to the iso-propyl methyls

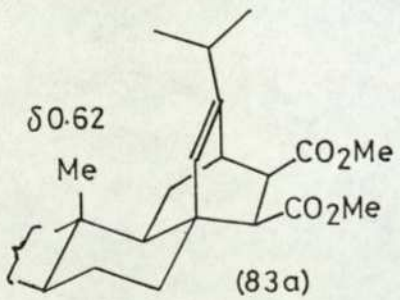


(81)

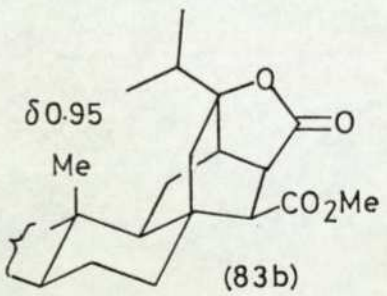


(82)

occurred at δ0.72. This, rather high, value is attributed to the shielding of the protons in question by the enolic double bond. Long-range effects of this nature have been observed in a variety of rigid systems.[70] Particularly illuminating is the case of the steroid derivatives (83a) and (83b)



(83a)

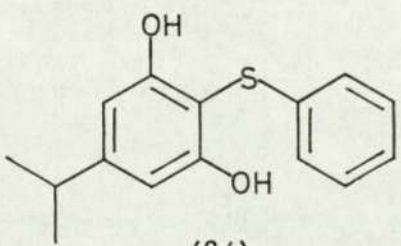


(83b)

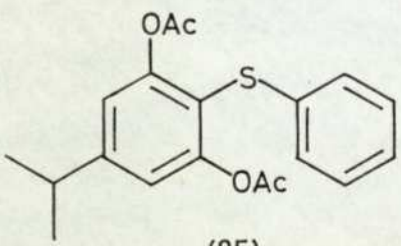
These findings provide independent evidence for the trans-diaxial conformation (82). Consequently, this corroborates all of the previously made structural assignments, arrived at through the consideration of the anisotropy of the sulphinyl group.

Thermolysis of the cyclohexanedione (81) gave, unexpectedly, another minor product in addition to 5-iso-

propyl resorcinol. The i.r. spectrum of the by-product closely resembled that of the resorcinol but for the additional absorptions at 740 and 690 cm^{-1}, which suggested a mono-substituted benzene ring. The n.m.r. spectrum confirmed this, showing a phenyl multiplet at δ6.8-7.2. Two exchangeable protons, a two-proton singlet at δ6.38, and an iso-propyl group with the methine multiplet occurring at δ3.44 completed the picture. Clearly, a mono-substituted phenyl moiety has been appended to the resorcinol nucleus. Since this could only be the phenylthio group, the structure (84) was assigned. The 2-substituted, rather than the 4-substituted, resorcinol seems the more likely alternative since the ring protons resonated as a sharp singlet, and the aromatic pattern was well defined, implying free rotation about the two C-S bonds. The compound gave the diacetate (85), on treatment with acetic anhydride in pyridine. In the n.m.r. spectrum the two-proton singlet became part of



(84)



(85)

the, now complex, aromatic pattern. This increased complexity presumably reflects some restriction to free rotation imposed on the sulphide (85), and in a sense confirms the structural assignment. In the 4-substituted case the change from the hydroxy to the acetate function would be expected to have a less pronounced effect.

Some confusion exists in the literature regarding the physical properties of 5-iso-propyl resorcinol. The compound, as obtained through an extensive, and vigorous, modification of 3,5-dimethoxy benzoic acid had a melting point of 112°C.[71] In a more recent, total synthesis, an oil was reported.[16] The oil prepared in the present work was therefore subjected to mass spectrometric analysis.

The major fragmentations, leading to the relatively abundant ions at m/e 137 and m/e 124, were confirmed by the presence of meta-stable peaks (Fig. 10).

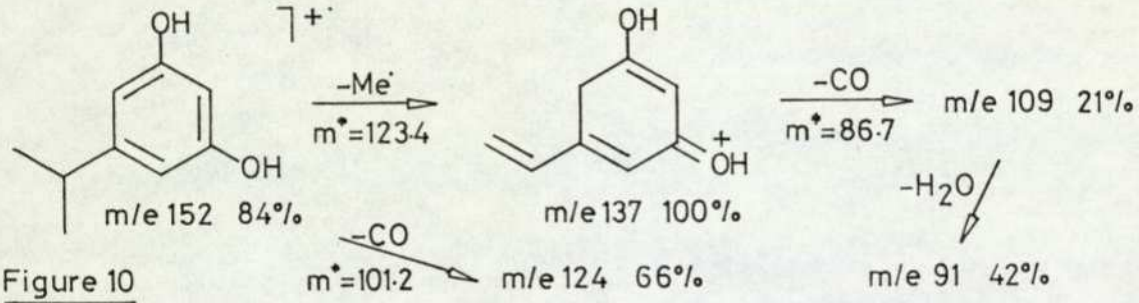


Figure 10

The loss of carbon monoxide is characteristic of phenolic compounds, although in this case 28 mass units could correspond to C_2H_4. Other distinctive peaks at m/e 91, 81, 69, as well as the correct accurate mass leave no doubt as to the authenticity of the sample.

It is assumed that the sulphide (84) was derived from a further reaction of the initially formed resorcinol, with one of the disproportionation products of phenylsulphenic acid. The identification of the electrophilic phenylthio-species should allow a refinement of the experimental conditions which would suppress, or enhance, this side reaction.

The reaction of MPSA with 1-acetyl-1-cyclohexene (Entry 7) was particularly inefficient. Under the usual conditions only trace amounts of the intermediate appeared to form. This was deduced from the characteristic change in the n.m.r. spectrum, of the acidic products, which occurred on thermolysis. However, the monitored signals were minor, and no concrete evidence can be presented, as the aromatic product was not isolated.

The starting ketone was largely recovered in this reaction.

The failure of the initial Michael addition probably reflects the moderate acceptor character of the enone. Even with, the more reactive, malonates and acetoacetates only average yields of the adducts have been realised.[72] Another adverse factor could be the geometry of the Michael product. If a trans-diaxial conformer is formed, the energy required to bring about the cyclisation may be sufficiently large to make the retro-Michael reaction a more favourable process.

The novel synthesis of 5-substituted resorcinols can be seen to be a fairly general reaction. The only limitation appears to be due to the steric effects, which will obviously affect any Michael-type reaction.[16,19,72] Therefore it seems unlikely that 5-tert-alkyl resorcinols could be prepared by this method. On the other hand, the ready availability of the starting materials and the simplicity of the experimental procedure, make this one-step process particularly attractive. The reaction conditions are sufficiently mild to allow the preparation of sensitive

compounds in respectable yields. These could be undoubtedly improved by the modifications suggested at the end of the chapter. Perhaps the single most important discovery though, was the ready interception of the cyclohexanedione intermediates, a novel class of compounds of considerable synthetic potential. One particularly exciting application could be the synthesis of optically active synthetic intermediates. We have seen that the four diastereoisomeric enol ethers, obtained by methylation of the olivetol cyclohexanedione, are readily separated and identified. The same reaction, if carried out with optically active MPSA, would give four separable enantiomers. Reductive removal of the sulphinyl group should furnish the two epimers of the valuable 5-substituted cyclohexanedione enol ethers. These could, of course, be modified further. In this context, the recently described preparation of an optically active arylsulphinylacetate is of interest, as it does not involve resolution.[73] It was found that methyl p-tolyl sulphide was oxidised stereospecifically to pure (+)R- or (-)S-methyl p-tolyl sulphoxides by Mortierella isabellina and Helminthosporium sp. respectively. The sulphoxides were then easily converted into optically pure t-butyl (p-tolylsulphinyl)acetates.

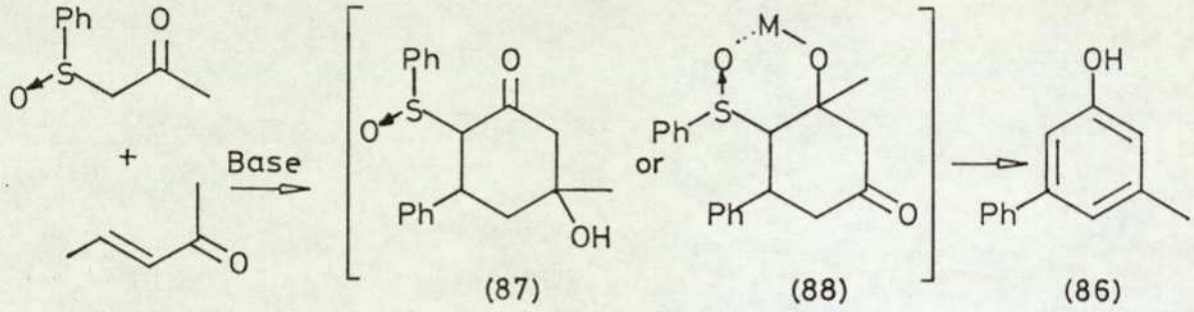
The success of the resorcinol synthesis prompted the investigation of some, conceptually similar, reactions.

Synthesis of phenols

As noted earlier, phenylsulphinyl acetone (PSA) failed to react with α,β-unsaturated esters. This was attributed

to the low reactivity of both components. Therefore replacing the Michael acceptor with an α,β-unsaturated ketone should result in a reaction which would eventually produce phenols instead of resorcinols.

As anticipated the condensation of PSA with benzylidene acetone (Scheme 12), under the usual conditions, proceeded

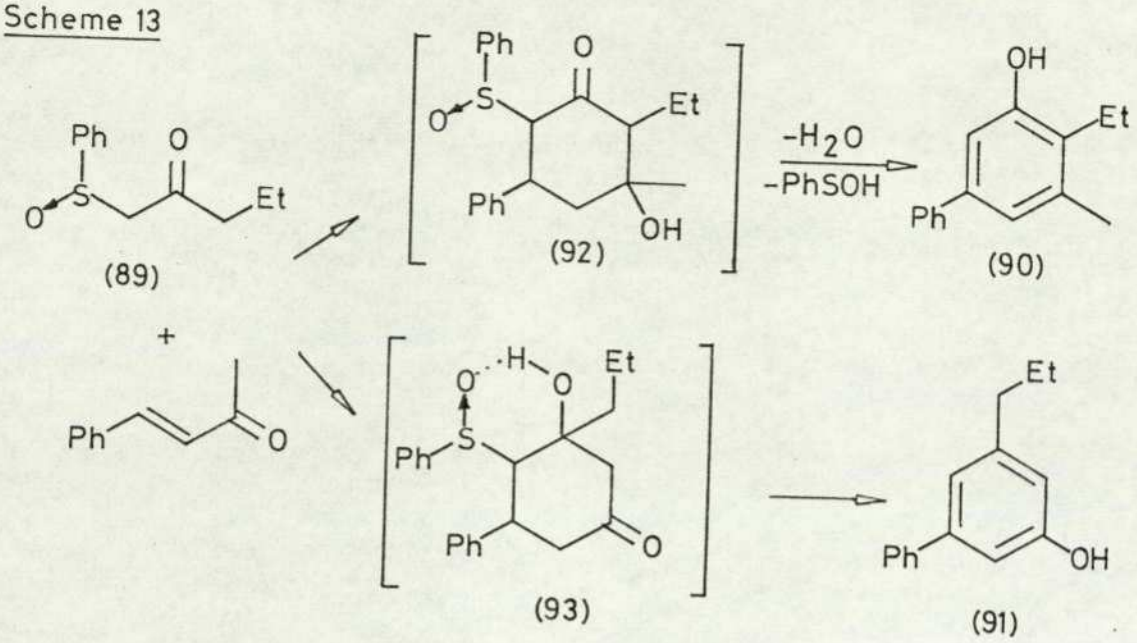


Scheme 12

smoothly to yield 60% of 3-phenyl-5-methylphenol (86). Presumably the reaction proceeds through intermediates such as (87) and/or (88). As neither of the two possible cyclohexanones was characterised, the mode of cyclisation, of the initial Michael adduct, was uncertain since both (87) and (88) would give the same aromatic product. The cyclohexanone (87) should be preferred for steric reasons alone. However, (88) might be stabilised by chelation with the counter ion.

In order to establish whether the phenylsulphinyl group was controlling the direction of the cyclisation 1-(phenylsulphinyl)-2-pentanone (89) was prepared and reacted with benzylidene acetone, under identical conditions (Scheme 13). The only isolated product was 2-ethyl-3-methyl-5-phenylphenol (90). The isomeric 3-phenyl-5-propylphenol (91) could not be detected. This implied that the reaction

Scheme 13



proceeded exclusively through the cyclohexanone (92). It would appear, therefore, that the relative stabilities of (92) and (93) do not play a part in the reaction; rather the sulphoxide determines which intermediate is formed.

A possible explanation for this regiospecificity can be proposed if the relative anionic stabilities are considered (Fig. 11). The initially generated Michael

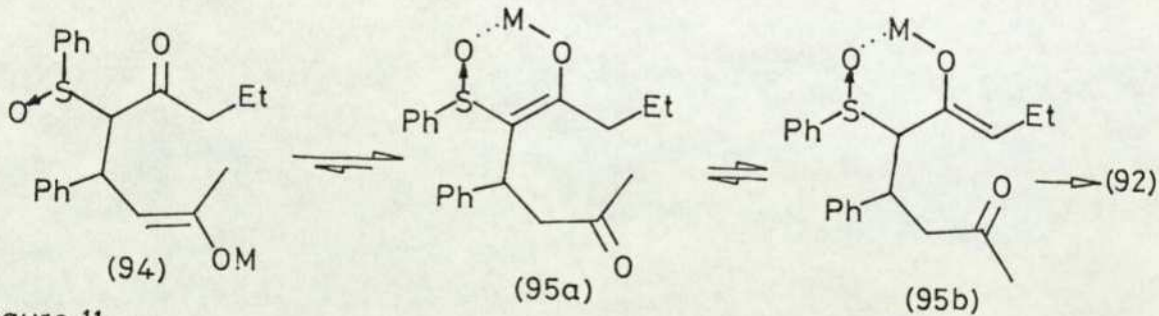
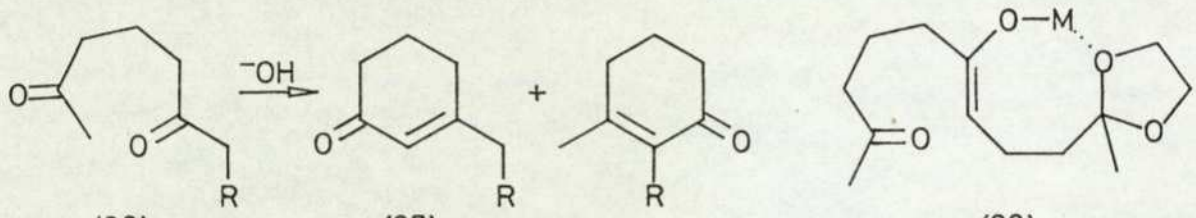


Figure 11

adduct anion (94) is clearly less stable than (95), into which it can be rapidly converted by an intramolecular proton transfer. The success of the cyclisation is attributed to the ready equilibration between (95a) and (95b). This is a reasonable assumption since the former

can be thought of as a vinylic sulphoxide with a tetra-substituted double bond, whilst the latter is a more favourable allylic sulphoxide with a tri-substituted double bond. The anion (95b) is clearly ideally set-up for the aldol reaction.

A comparison with the base-catalysed reaction of simple 1,5-diketones will serve to emphasise the directing effect of the phenylsulphinyl group. The mode of cyclisation of diketones (96) was found to depend on the nature of R and on the temperature.[74] The ratio of the tri-substituted (97)

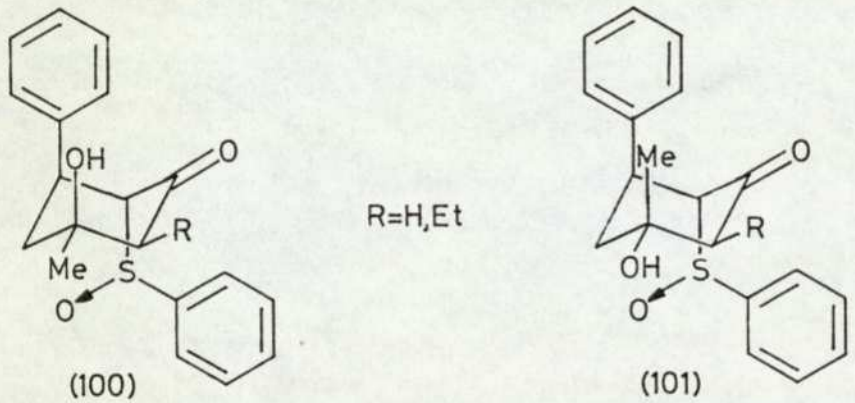


(96) (97) (98) (99)

to tetra-substituted product (98) was close to unity, in favour of (97), when R was a straight chain and the reaction was performed at room temperature. Branching in the R group, close to the ketone function, tended to favour the tri-substituted product. However, when R contained a dioxolan group, δ- to the carbonyl, (98) became the preferred isomer. This was interpreted in terms of additional stabilisation of the enolate (99) by the ketal oxygens. At elevated temperatures the tetra-substituted product was favoured. Under these conditions though the cyclohexenones (97) were converted to (98) via retro-aldol reaction. In the case of (92) such equilibration is, of course, impossible.

In the reaction of PSA and benzylidene acetone a small amount of a very polar solid could be isolated. The

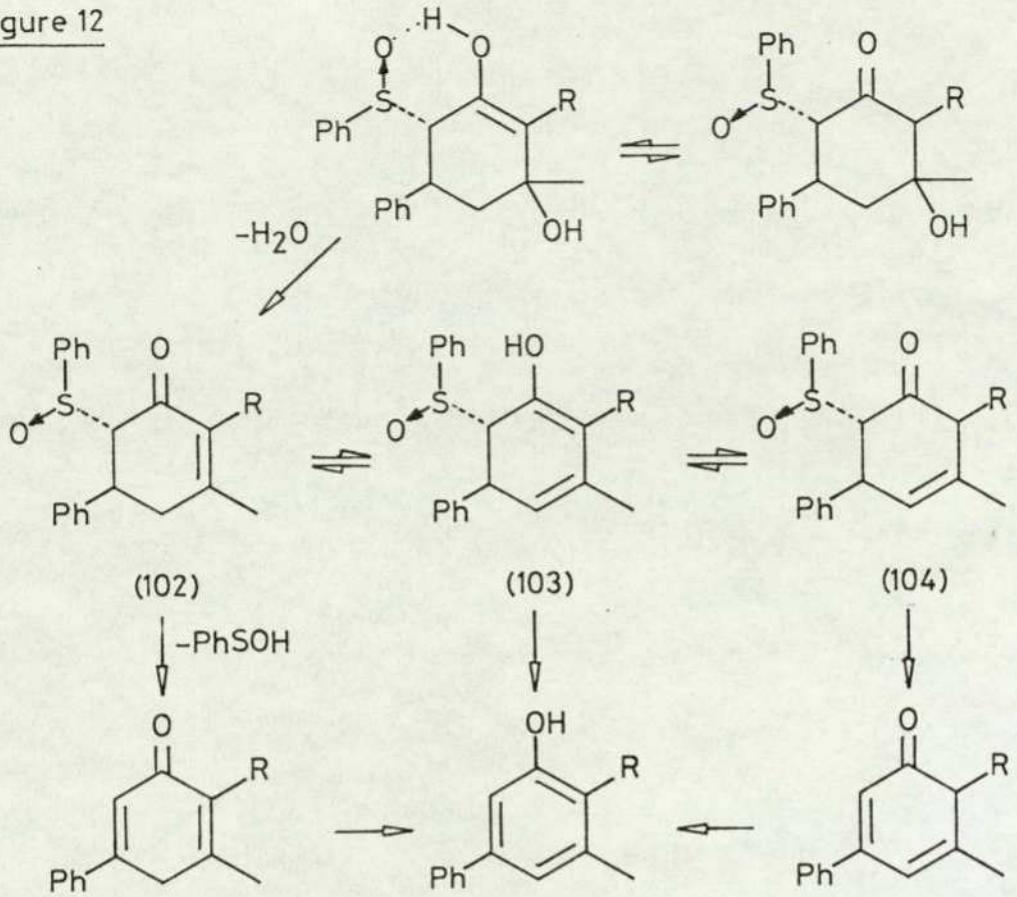
compound decomposed rapidly to the phenol (86), thus confirming the existence of a phenylsulphinyl-containing intermediate. The instability of the presumed cyclohexanones (87) and (92) can be rationalised in several ways. The absence of hydrogen bonding, or chelation with the counter ion, which stabilised the corresponding cyclohexanediones in the resorcinol series could be one of the main factors. Assuming the overwhelming preference of the phenylsulphinyl group for adopting the axial orientation also applies in this case, the two intermediates could be depicted as (100) and (101). The resultant 1,3-diaxial interaction between



(100) (101)

the 3-phenyl and the 5-hydroxy, or 5-methyl groups, would greatly accelerate the rate of dehydration or of elimination of the sulphenic acid. A tentative mechanism, which also assumes that dehydration occurs first, is proposed in Figure 12. The cyclohexenone (102) can eliminate phenylsulphenic acid directly, since in the absence of hydrogen-bonded stabilisation the dipole-dipole repulsion would force the sulphoxide oxygen away from the carbonyl.[75] Alternatively, the basic ambience could lead to further enolisation (103) and equilibration with the β,γ-unsaturated isomer (104).

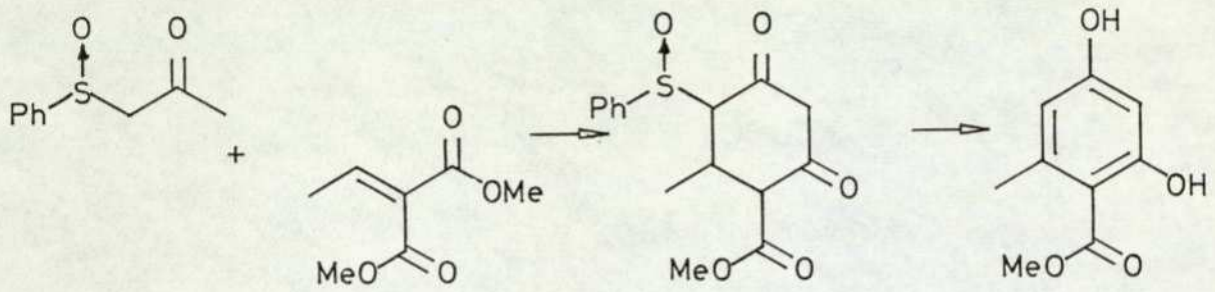
Figure 12



Either (103) or (104) would be expected to eliminate phenylsulphenic acid faster than the cyclohexenone (102). The dienolate (103) would force the ring towards planarity, thus creating the ideal transition state geometry, whilst (104) would provide extra allylic activation to the benzylic proton, also accelerating the rate of sulphoxide fragmentation. The elucidation of the actual sequence of events, however, must await the isolation and characterisation of the intermediates. The fact that an intermediate was observed suggests that with a few straightforward modifications this should be possible. By analogy with the resorcinol series the use of alkyl, rather than aryl, enones should lead to less labile compounds. Additional stability would be provided by replacing the α-phenylsulphinyl ketones with, say, α-methylsulphinyl analogs.

Reactions with dimethyl ethylidene malonate (105) and with ethyl benzylidene acetoacetate (110)

Since the reaction of β-keto sulphoxides with benzylidene acetone occurred readily, it was anticipated that an analogous condensation of PSA with dimethyl ethylidene malonate (105) would give methyl orsellinate (106) (Scheme 14). The outcome, however, was not wholly satisfactory.



Scheme 14 (105) (107) (106)

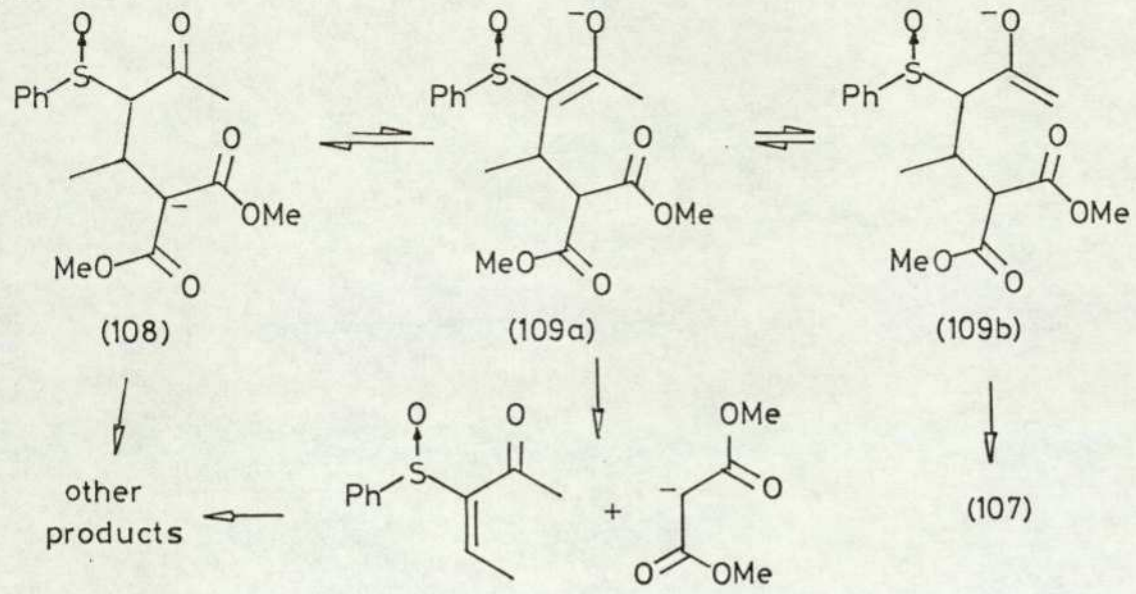
Although PSA reacted rapidly with the unsaturated diester, under the standard conditions, complex mixtures were the result, and little methyl orsellinate could be detected. Performing the reaction at room temperature (magnesium methoxide/methanol) gave products of R_f similar to the starting sulphoxide, which could have been the initial Michael adducts. Raising the temperature to reflux, in an attempt to effect the cyclisation, caused the appearance of numerous non-polar spots. The n.m.r. spectrum of the crude mixture indicated that neither methyl orsellinate (106), nor the cyclohexanedione (107) were formed. The mixture was not investigated further, but the simplicity of the spectra points to their trivial nature. The use of benzyltrimethylammonium methoxide as the base only catalysed the Michael addition of methanol to the diester. The main problem appeared to be

the instability of (105) to the basic conditions, reflecting the great acidity of the γ-hydrogens and the propensity to accept any nucleophile.

More interesting results were obtained with the sodium hydride/THF system. When the diester was added to the preformed PSA enolate at -60°, and the mixture allowed to reach room temperature, the crude product did contain the orsellinic ester. In addition, the usual double extraction procedure gave a small amount of what appeared to be the cyclohexanedione (107). The n.m.r. spectrum was extremely complex, which is not surprising if we consider the number of possible diastereoisomers and keto-enol equilibria. Thermolysis of the acidic fraction resulted in a dramatic simplification of the spectrum as the complex pattern gave way to the signals attributed to methyl orsellinate. The intermediacy of a compound such as (107) was therefore established. Despite this improvement the overall yield of the aromatic compound was disappointingly low.

The relative failure of this reaction can be attributed to the inefficiency of the cyclisation step. Consideration of the anionic stabilities once again provides an explanation (Fig. 13). Unlike the phenol series, the initially formed Michael adduct anion (108) is more stable than (109). Consequently, the required equilibration is hindered and other reactions are allowed to develop. Furthermore, (109a) can eliminate the dimethyl malonate anion in a <u>retro</u>-Michael reaction, again increasing the number of possible side-reactions. Despite these complications, the formation of

Figure 13

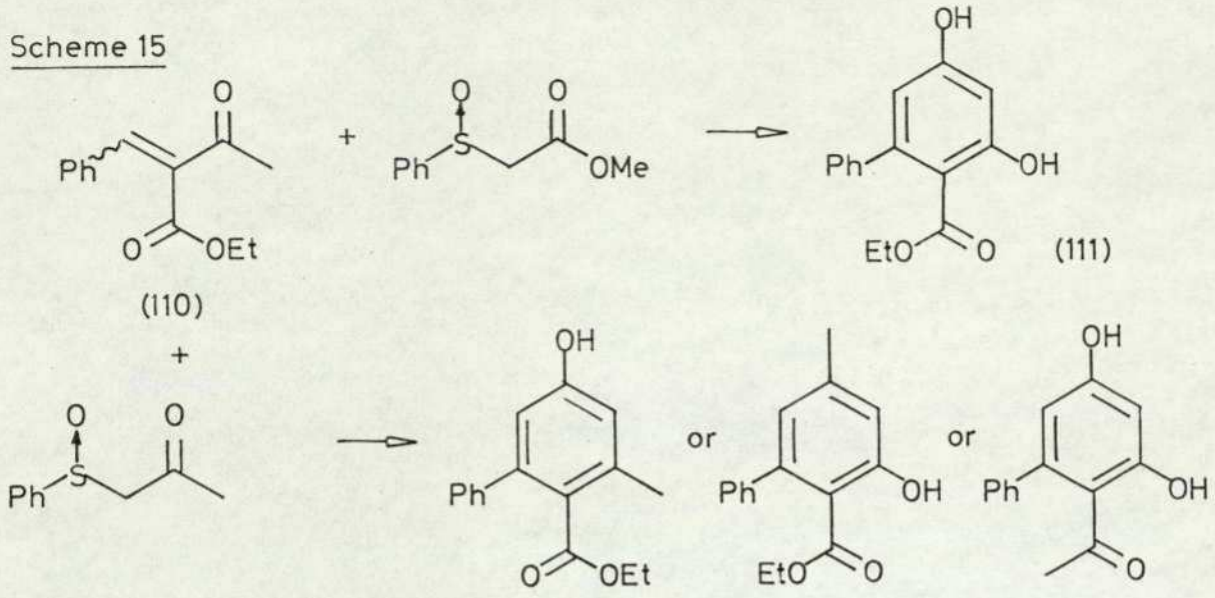


the orsellinic ester (106) indicates that juggling with the experimental conditions could improve the yields. The reaction may prove useful for arylidene and alkylidene malonates with no acidic γ-hydrogens. With these substrates, the formation of side-products resulting from the initial proton transfer processes would be eliminated.

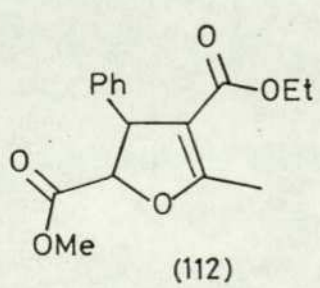
If relative anionic stability is the chief factor determining the course of these reactions then the generation of an even more stable anion, in the Michael addition step, should completely suppress the formation of aromatic products. In order to check this contention, ethyl benzylidene aceto-acetate (110) was selected as the Michael acceptor. The keto ester was chosen because it could give rise to aromatic products with both MPSA and PSA (Scheme 15), and because it lacks the acidic γ-protons.

The reaction of the preformed sodium enolate of MPSA with (110) appeared to give little, if any, of the resorcinol (111). The major product was rather non-polar on t.l.c.,

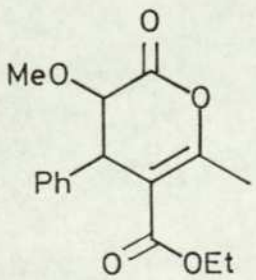
Scheme 15



running close to the starting material. The ^{1}H n.m.r. spectrum showed a distinctive one proton doublet at δ4.90 and a broad doublet at δ4.48 also integrating for one proton. A vinylic methyl group at δ2.40 and signals due to a phenyl, a methoxy and an ethoxy group completed the picture. Irradiation of the broad doublet at δ4.48 sharpened the vinyl methyl signal and reduced the doublet at δ4.90 to a singlet. Conversely, irradiation of the latter doublet sharpened the signal at δ4.48 but had no effect on the methyl resonance at δ2.40. The i.r. spectrum exhibited strong absorptions at 1755, 1700 and 1650 cm^{-1}, suggesting the presence of a saturated ester, an unsaturated ester and an enol ether. The evidence indicated loss of the phenylsulphinyl group and pointed to two possible structures (112)

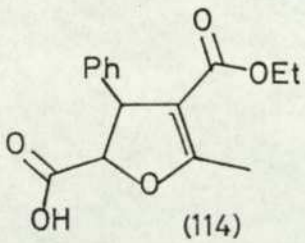


(112)

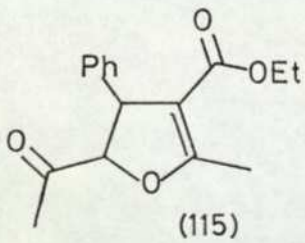


(113)

and (113). Of these the dihydrofuran was intuitively preferred, not least because its formation could be more readily explained. The compound gave a weak molecular ion at m/e 290, and the accurate mass measurement established the formula as $C_{16}H_{18}O_5$. The spectrum was complex, however, and no distinctive fragmentation pattern could be recognised. The dihydrofuran structure (112) could be unambiguously assigned after it was noticed that the compound was converted to an acid. The saponification occurred on standing at room temperature. The ^1H n.m.r. spectrum of the acid was similar to that of the starting ester, except that the methoxy singlet was replaced by an exchangeable proton. The i.r. spectrum showed the characteristically broad-OH absorption at 3400-2500 cm^{-1}, and the 1755 cm^{-1} band, of the ester, was replaced by an absorption at 1720 cm^{-1}. These changes are consistent with the hydrolysis of (112) giving (114).



(114)



(115)

Furthermore, methylation of the acid (114) gave back the dihydrofuran (112) confirming the simple relationship. The relative stereochemistry of (112) and (114) is unknown.

The reaction of PSA with ethyl benzylidene acetoacetate gave a result analogous to the MPSA experiment. The ^1H n.m.r. spectrum of the crude product showed the distinctive pattern of the dihydrofuran (112), with an important difference; the methoxy signal of the latter was replaced

by a methyl singlet at δ2.18. This observation corroborated further the dihydrofuran structure (112) and enabled the representation of the product as (115). Although the compound was not isolated, there seems no reason to doubt the accuracy of this assignment.

Finally, the reaction of (110) with methyl (phenylsulphonyl)acetate also furnished the dihydrofuran (112), as evidenced by t.l.c. and n.m.r. analysis. The yield in this case was very low; the main product appeared to be the straightforward Michael adduct.

The dihydrofurans (112) and (115) apparently arise as the result of a simple nucleophilic displacement of the phenylsulphinate by the acetoacetate anion. The actual mechanism, however, is open to speculation for the following reasons. The dihydrofurans were the major products after the reaction mixtures were refluxed. The condensation of MPSA with (110) at room temperature gave products of R_f values similar to the starting sulphoxide. Apparently these were not the straightforward Michael adducts as the n.m.r. spectrum, of the crude mixture, showed the signal due to the methyl ester to be absent. Instead, a group of singlets in the range δ3.3-3.4 was observed. The nature of these products was not determined as their instability on silica prevented ready isolation. Further, the same reaction when carried out in the presence of an excess of sodium hydride, i.e. conditions which should suppress the dihydrofuran formation, gave the acid (114) in approximately 20% yield, as determined from the n.m.r.

integral. The saponification, caused by the hydroxide present in sodium hydride, presumably occurred after the generation of the dihydrofuran, although this assumption must remain tentative. A mechanism, consistent with the above observations, is outlined in Figure 14. The proposed,

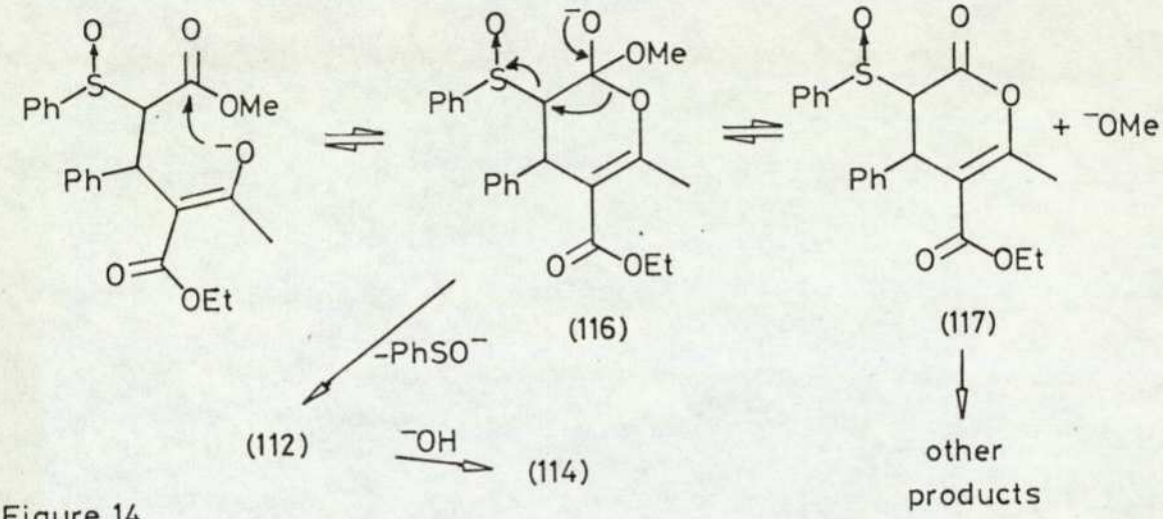


Figure 14

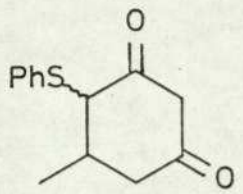
initially formed, dihydropyran derivative (116) could undergo either ring contraction, with concomitant expulsion of the phenylsulphinate anion, or elimination of methoxide to give the dihydropyrone (117). The latter intermediate can be converted to the dihydrofurans and to the other, unidentified products.

The reactions described thus far indicate that α,β-unsaturated ketones are the optimal Michael acceptors for PSA and MPSA, if phenols or resorcinols are the required products. The investigations were confined to two types of activating groups only, viz. ketones and esters. Clearly, there is a considerable scope for extending this type of reaction to systems with other activating groups, such as nitriles, aldehydes and so on. The use of nitro olefins as

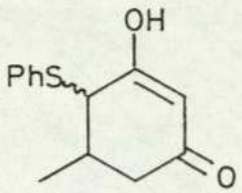
Michael acceptors[76] in tandem with β-keto sulphoxides would be particularly interesting as it could lead to cyclopentanone or cyclopentenone derivatives. The Michael reaction remains one of the most powerful tools of a synthetic chemist, partly because of the variety offered by the various activating groups, and also because the primary adducts can be frequently converted into carbocyclic and heterocyclic compounds.[72] The use of a sulphinyl-containing active methylene component extends the range further. As we have seen, the presence of the sulphoxide provides a remarkable degree of regio- and stereo control, and, from the analytical point of view, enables detailed structural assignments. These aspects are clearly illustrated by comparing the reactions of PSA, and phenylthioacetone with methyl crotonate.

The relative acidities of the protons α- to sulphur-containing groups follow the order $ArSO_2$ > ArSO > ArS.[77] Consequently, the carbanion stabilised by a sulphide would be expected to be more reactive than that stabilised by a sulphoxide. In agreement with theory, the reaction of phenylthioacetone with methyl crotonate took place much more readily than the analogous reaction of PSA. It will be recalled that the latter could only be brought about under forcing conditions (2 days in refluxing THF). The sulphide reacted at room temperature, and the degree of conversion, after 2 days, was significantly higher (40%). Two major, very polar products were formed. The more polar material was identified as a mixture of cyclohexanediones represented by the covalent structure (118). The i.r. spectrum showed

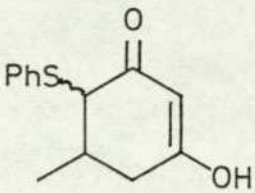
the characteristic features of cyclic 1,3-diketones, -OH absorption at 3300 cm^{-1} and a broad band centred at



(118)

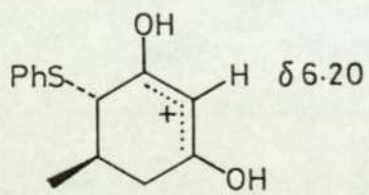


(119a)

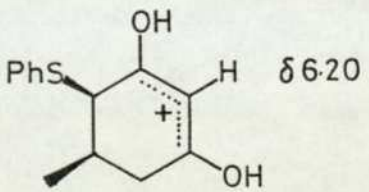


(119b)

1590 cm^{-1}. The n.m.r. spectrum was very complex exhibiting at least four doublets, integrating for three protons, in the region δ1.04-1.36. The most distinctive feature was the presence of two vinylic singlets at δ5.52 and δ5.62 totalling approximately 3/4 of a proton. These observations are consistent with the existence of two enolic forms, (119a) and (119b), as well as the cis- and trans-isomers. Addition of a twenty-fold excess of trifluoroacetic acid simplified the spectrum, which now showed two doublets at δ1.32 and δ1.44, total three protons, and a one-proton singlet at δ6.20. The signals are, presumably, due to the fully protonated forms, (120a) and (120b), of the trans- and cis-isomers respectively (Fig. 15).



(120a)



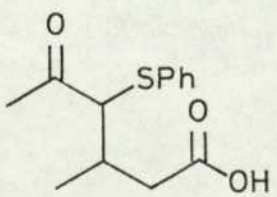
(120b)

Figure 15

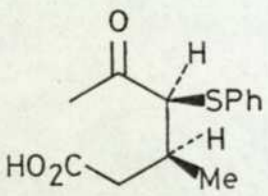
The ratio of (120a) to (120b) was approximately 3:2, as calculated from the relative intensities of the two methyl doublets. It may be noted that the syn- phenylthio group causes a down-field shift of 0.1 p.p.m. The syn-

phenylsulphinyl moiety caused down-field shifts of the order of 0.5 p.p.m. The latter group also determined the direction of enolisation of the cyclohexanedione intermediates. In sharp contrast, (118) has no preferred enol form.

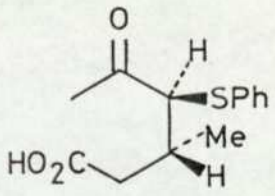
The second product had a much simpler n.m.r. spectrum. Only two methyl doublets at δ1.08, 1.7 of a proton, and at δ1.30, 1.3 of a proton, were observed. The olefinic signals of (118) were absent. A distinctive three-proton singlet at δ2.30 and one exchangeable proton at δ11.8 were the other, significantly different, features. The i.r. spectrum indicated a keto acid judging by the presence of a broad band at 3300-2600 cm^{-1} and a carbonyl absorption at 1700 cm^{-1} with a shoulder at 1715 cm^{-1}. On this evidence the structure (121) was assigned. Assuming that the deshielded methyl doublet, at δ1.30, is due to the erythro-isomer (122a), the



(121)



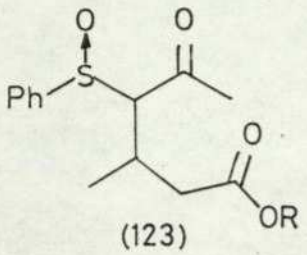
(122a)



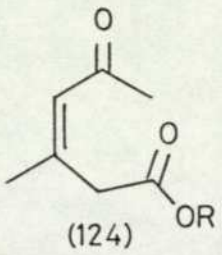
(122b)

threo-isomer (122b) is seen to be the preferred compound. The ratio of (122b) to (122a) was approximately 1.3:1, and it corresponds closely with the ratio of the trans- to cis-cyclohexanediones (118). The formation of the keto acid (121), in itself unexceptional, presumably reflects the reluctance to cyclise of the corresponding keto ester. It is worth noting that, in the reaction of PSA with methyl crotonate the analogous acyclic compounds, (123) or (124)

(R = Me or H), if formed could not be detected by n.m.r. The implication is that the phenylsulphinyl group assists



(123)



(124)

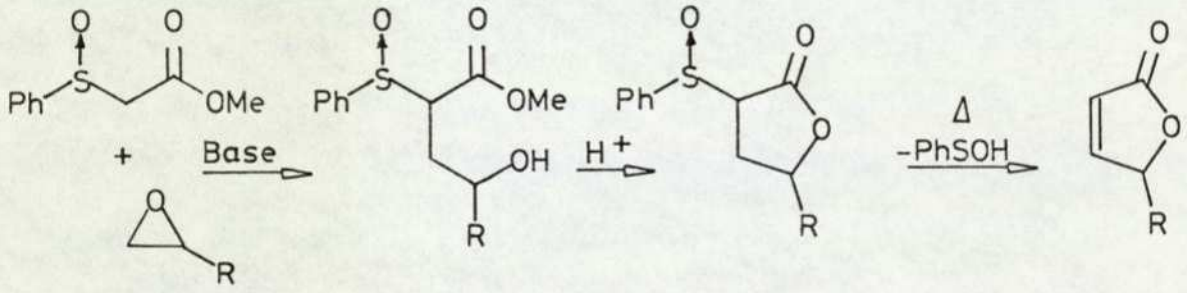
the cyclisation of the initial Michael adduct (123, R = Me), or that the elimination of phenylsulphenic acid leads to Z (124), which again has the correct geometry for the intramolecular Claisen condensation. In either event orcinol is the observed product.

The relatively low reactivity of PSA, and MPSA, could be perhaps overcome by using the methylsulphinyl analogs. This modification should enhance the nucleophilicity of the carbanions, and the reduction in the steric bulk of the reagent should accelerate the rate of reaction with hindered acceptors. As mentioned earlier, the use of the methylsulphinyl group would retard the thermal fragmentation of the resultant sulphoxides, thus stabilising the interesting cyclohexanedione and cyclohexanone intermediates. Further experimentation with the counter ions should also be of interest (see Chapter 3). For example, the potassium enolates of α-methylsulphinyl ketones were found to be alkylated more rapidly than the sodium salts.[56]

CHAPTER 3

The chief attraction of the α-sulphinyl ketones and esters is the incipient oxidation level which can be utilised at the required stage of a synthesis by elimination of phenylsulphenic acid. The sulphinyl group is also a powerful controlling factor and is capable of other, remarkable transformations.[78] These attributes make its use, as an activating group, particularly alluring.

Numerous synthetic projects could be executed, in theory at least, with the aid of a sulphoxide. One such scheme appeared to be a simple preparation of butenolides (Scheme 16).



Scheme 16

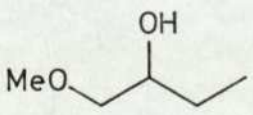
A conceptually similar approach, utilising the dianion of phenythioacetic acid to open the epoxide, followed by lactonisation, oxidation and elimination of the sulphenic acid, has been described.[79] Nevertheless, it seemed that the proposed route would be an improvement, particularly in view of the potential for the synthesis of optically active compounds. Unfortunately, the carbanion derived from MPSA proved virtually inert towards 1,2-epoxybutane under various conditions (Table III).

The use of n-butyl-lithium (Entry 1) led to the incor-

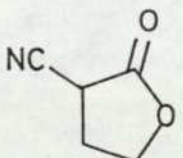
Table III

1.	n-BuLi/THF/25-70°	6.	NaH/DMF/25°
2.	LiDIPA/THF/25-70°	7.	NaOMe/HOMe/25-70°
3.	NaH/THF/25-70°	8.	$Mg(OMe)_2$/HOMe/25-70°
4.	NaH/THF/18-crown-6/25-70°	9.	$Et_3N/ZnCl_2$/25°
5.	NaH/THF/HMPA/25-70°		

poration of the butyl moiety, apparently as the result of the initial nucleophilic attack on the sulphoxide. The use of lithium di-isopropylamide suppressed that reaction, but no desired products could be detected. Attempts to generate the naked anion (Entries 4, 5 and 6) did not result in a significant improvement, although some incorporation of an alkyl residue could be detected from the n.m.r. spectra of the crude products. The starting sulphinyl ester was largely recovered. Methanolic sodium methoxide led to the formation of the hydroxy ether (125).



(125)

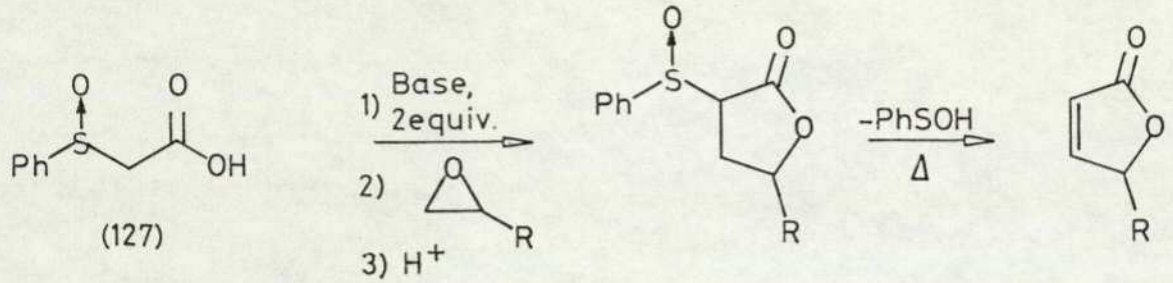


(126)

Under identical conditions ethyl cyanoacetate and propylene oxide gave the lactone (126).[80] It would appear, therefore, that the MPSA anion is too stabilised and hence not reactive enough to open the epoxide.

In order to enhance the reactivity, whilst retaining the

advantages proffered by the sulphinyl group, the reaction of the dianion of phenylsulphinylacetic acid (127) was attempted (Scheme 17). Also in this case, the dilithio salt of the



Scheme 17

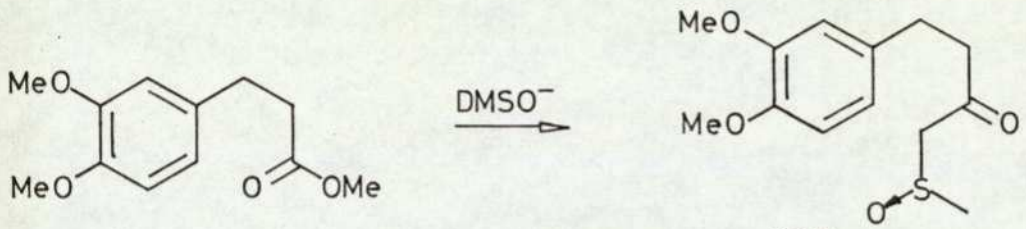
acid proved unreactive towards the epoxide. The effect of counter-ions other than lithium was not investigated. The use of more electro-positive metals may have been advantageous, though it seems doubtful that a practical method could be developed.

Alkylations of the dianion of phenylsulphinylacetone and some transformations of the products

The β-keto sulphoxide (89), used to determine the direction of cyclisation of the intermediates in the synthesis of phenols, was prepared by alkylation of the dianion of PSA with ethyl bromide. The generation of the dianion was best accomplished using lithium di-isopropylamide.[81] The initially attempted, mixed base procedure, i.e. sodium hydride followed by n-butyl-lithium, described by Grieco and Pogonowsky,[82] was found unsatisfactory. The alkyl-lithium attacked the sulphoxide in a reaction similar to that observed with MPSA (page 124). This problem was also reported by the American authors in a subsequent publication.[83] When the sodium

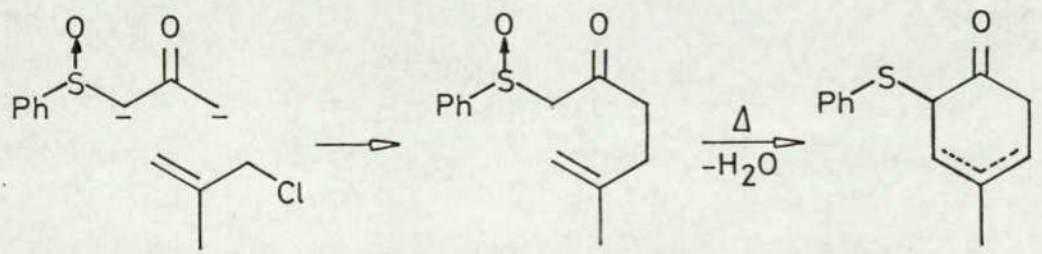
enolate of an α-phenylsulphinyl ketone was treated with n-butyl-lithium, phenyl-lithium was displaced and the α-butylsulphinyl ketone was formed. Furthermore, the dianion was then generated α'- to the sulphoxide rather than in the desired γ-position, leading to numerous products.

In the Review section the intramolecular trapping of Pummerer intermediates by carbon nucleophiles, resulting in cyclic compounds, has been described. The required β-keto



(128)

sulphoxide precursors, such as (128), have been prepared by the reaction of dimsyl sodium on the corresponding ester.[84] The efficient alkylation of the PSA dianion suggested an alternative method for the synthesis of similar keto sulphoxides, and prompted the investigation of the cyclisation reaction, with a simple double bond as the nucleophile (Scheme 18). Additional interest was provided by a recent report that α-phenylsulphinyl esters and ketones underwent an analogous, intermolecular Pummerer reaction, with xylene and anisole, on heating alone.[85]

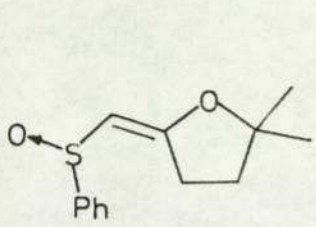


Scheme 18 (129) (130)

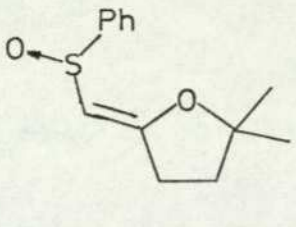
The alkylation of the dianion with methallyl chloride gave the expected hexenone (129), in 68% yield after chromatography. Attempted distillation of the crude product at 100°C led to extensive decomposition. The purified keto sulphoxide (129), however, was recovered unchanged after 24 h in refluxing benzene or toluene. Addition of a catalytic amount of toluene-p-sulphonic acid and heating the benzene solution overnight gave a complex mixture from which p-cresol could be isolated in low yield (10%). Clearly this treatment was too vigorous. Although the required C-C bond must have formed, the intermediate cyclohexenones (130) presumably eliminated thiophenol to give the aromatic product.

The use of trifluoroacetic acid gave an unexpected result. The reaction was performed at room temperature and its progress was conveniently monitored by n.m.r. spectroscopy. The AB quartet, due to the methylene group α- to the sulphoxide, and the characteristic methallyl signals disappeared at the same rate, indicating some form of interaction between these centres. The appearance of two olefinic resonances could have been attributed to the formation of a mixture of cyclohexenones (130). The puzzling feature of the reaction, as observed by t.l.c., however, was that the majority of products had R_f values similar to the starting sulphoxide. The expected Pummerer products should be non-polar. The attempted, chromatographic separation of the polar products was unsuccessful. Nevertheless, from the spectral data of the semi-purified mixture it would appear that it comprised the three cyclic ethers (131), (132) and

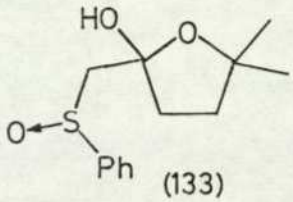
(133). These structures are tentatively postulated on the following evidence. The n.m.r. spectrum revealed two broad



(131)



(132)



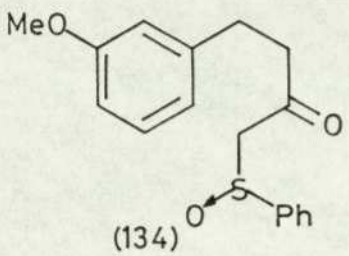
(133)

singlets at δ5.6 and δ5.2, assigned to the olefinic hydrogens of (131) and (132). These two signals together with an exchangeable, broad singlet at δ5.4 integrated for one proton. A group of singlets in the region δ1.25-δ1.50, total six protons, corresponds to the gem-dimethyl group. The remaining non-aromatic signals formed three complex multiplets centred at δ2.0, δ2.9 and δ3.2. The multiplet at δ3.2 could be attributed to the methylene α- to the phenylsulphinyl group in (133), the signals at δ2.9 were presumably due to the allylic protons in (131) (deshielding by the cis-sulphoxide) and the most intense multiplet at δ2.0 accounted for the remaining nuclei. The i.r. spectrum showed strong bands at 1630 (1610 sh), 1250 and 1050-1030 cm^{-1}, characteristic of enol ethers. The absorption at 1050-1030 cm^{-1} was very intense, due to the combination with S-O stretching. A band at 3300 cm^{-1} and a weak carbonyl absorption at 1705 cm^{-1}, possibly due to the open form of (133), were also observed.

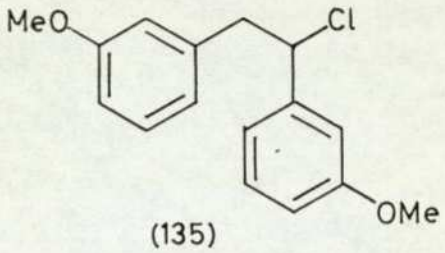
The reaction, although novel, was not investigated further as the yield was modest, and the synthetic utility appeared to be limited. It is possible that variation in the amount of TFA used would accomplish a more selective

transformation (two equivalents of TFA were used in the above experiment).

A system similar to the ones described by the Japanese workers[84] was also investigated. Alkylation of the dianion of PSA with m-methoxy benzyl chloride gave the required precursor (134), although the reaction was not as clean as



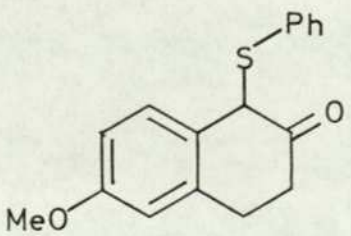
(134)



(135)

with the alkyl and allylic halides. A minor, less polar product whose n.m.r. spectrum showed a one-proton triplet at δ5.16 and a two-proton doublet at δ3.36 (J = 7 Hz), in addition to two m-methoxy phenyl groups was formed in, approximately, 15% yield. On these grounds the structure (135) was assigned. The formation of the by-product was probably due to the excess of the base employed to generate the dianion. This type of coupling of benzyl halides in the presence of strong bases is not uncommon.[86]

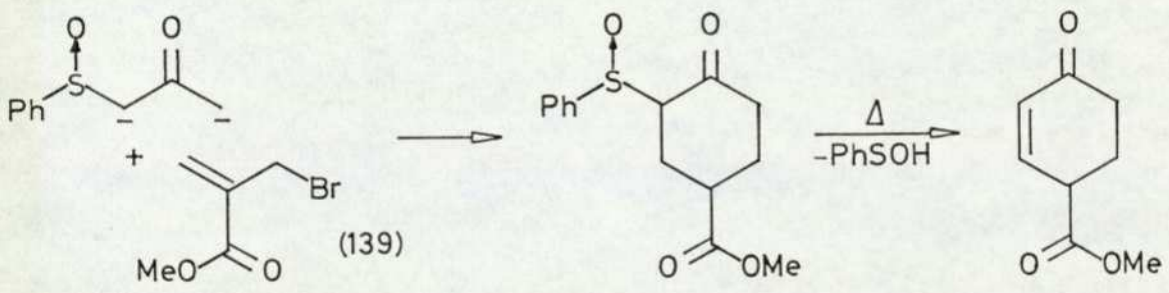
Thermolysis of the crude (134) in refluxing benzene led to the formation of some cyclised product (136), as evidenced



(136)

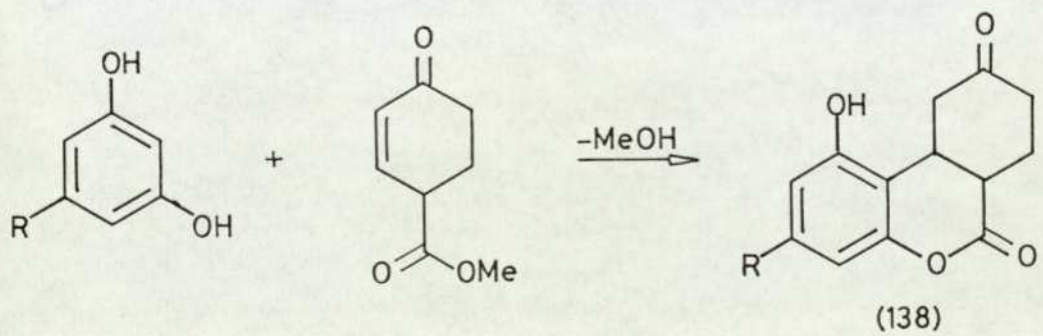
by the appearance of a singlet at δ4.64 in the n.m.r. spectrum of the crude mixture. This reaction was virtually suppressed when the pure keto sulphoxide (134) was subjected to the same conditions. Prolonged heating caused extensive decomposition of the starting material. From these observations it would seem that the Pummerer reaction cannot be brought about by heating alone. The sensitivity of this rearrangement to the catalytic presence of impurities has been noted.[87]

A reaction which promised to utilise both the anionic sites of PSA, as well as the built-in oxidant, is outlined in Scheme 19. The cyclohexenone (137) is of interest because



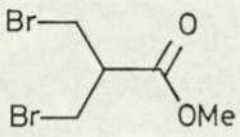
Scheme 19

its condensation with a 5-substituted resorcinol should give the tricyclic system (138). This benzopyrone derivative has

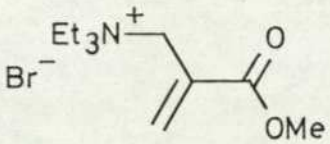


been shown to be a versatile intermediate in the cannabinoid field.[88] Surprisingly, the cyclohexenone (137) has not been synthesised.

The α-bromomethyl acrylate (139) has been widely employed, most notably by Lawton in bis-annulation of enamines.[89] The actual reagent used was the readily available[90] methyl dibromoisobutyrate (140), which was reacted with an enamine in the presence of triethylamine.



(140)



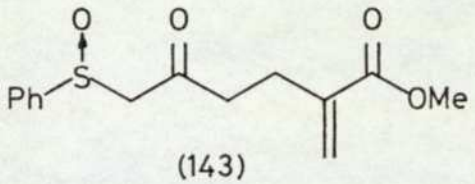
(141)

The acrylate (139) was assumed to have formed in situ.[89] Clearly this procedure could not be applied in the present case.

An attempt to generate the acrylate (139) by using one equivalent of triethylamine resulted in the recovery of exactly half of the starting material. The examination of the aqueous phase revealed that the remaining half has been converted to the salt (141). Evidently the very reactive allylic bromide (139) is immediately attacked by the amine. Presumably the salt (141) was the electrophilic species in Lawton's reactions. Unfortunately, triethylammonium bromide could not be readily removed from the mixture to allow the use of the salt (141), in lieu of the bromide (139), in the intended alkylation. The authentic acrylate was obtained by adding the dibromo ester (140) to lithium di-isopropylamide at low (-78^{o}) temperature.

Regrettably the alkylation of the dianion of PSA with (139) was unsuccessful. The bromomethyl acrylate proved too unstable in the strongly alkaline ambience; extensive polymerisation occurred even at low temperature. Neither

the phenylsulphinyl cyclohexanone (142) nor the cyclohexenone (137) could be detected. A small amount of the alkylation product (143) appeared to have formed, but could not be satisfactorily separated from the contaminant PSA. The n.m.r. spectrum of this mixture showed, in addition to PSA signals, the characteristic terminal olefin broad singlets at δ5.64 and δ6.22, a methoxy singlet at δ3.80 and a four-proton multiplet at δ2.5-2.9. The low yield and the

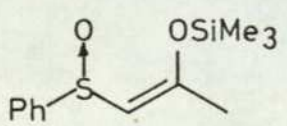


(143)

fact that the cyclohexanone (142) was not observed in the reaction mixture, implying that (143) does not cyclise readily, discouraged further investigation.

Synthesis and reactions of methyl 5-phenyl-2-phenylsulphinyl-pent-2-enoate (157)

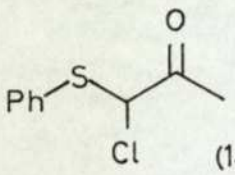
Whilst working on the condensation of PSA and ethyl benzylidene acetoacetate (110) an attempt was made to form the trimethylsilyl enol ether (144), in the hope that the subsequent reaction of such a derivative would suppress the formation of the dihydrofuran (115).



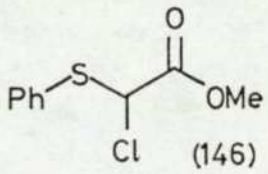
(144)

The sodium enolate of PSA was prepared in the usual way and quenched with an excess of trimethylsilyl chloride. The

keto ester (110) was then added and the mixture refluxed overnight. The t.l.c. behaviour and the n.m.r. spectrum of the crude products showed that, while the Michael acceptor remained unchanged, PSA had completely disappeared. In its place a single non-polar compound was formed which showed a one-proton singlet at δ5.50, a three-proton singlet at δ2.30 and a phenyl multiplet. The product gave a positive halogen test and the i.r. spectrum showed a strong band at 1720 cm^{-1} indicative of an α-chloro ketone. On this evidence it had to be the chlorosulphide (145). Not surprisingly, the initially yellow, unpleasant smelling oil rapidly turned brown on exposure to light and air. Although the mechanism



(145)

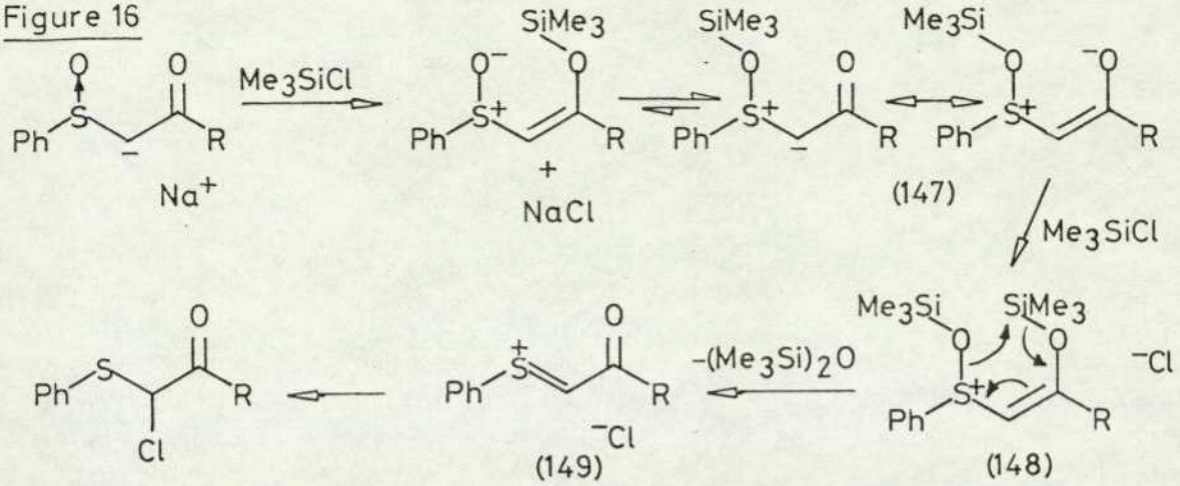


(146)

by which the chlorosulphide arises is uncertain, a tentative suggestion can be offered.

Treatment of lithium anions of simple sulphoxides with trimethylsilyl chloride is known to result in the sila-Pummerer rearrangement, which has been discussed in the Review section (page 33). In the light of those findings the following mechanism can be formulated (Figure 16). An important, additional piece of information is that treatment of the sodium enolate of MPSA with an excess of trimethyl-silyl chloride, under idential conditions, leads to the chlorosulphide (146) but the reaction is much more sluggish. This implies, perhaps, that the relative ease of formation of enolates from ketones, as compared with esters, is a

Figure 16

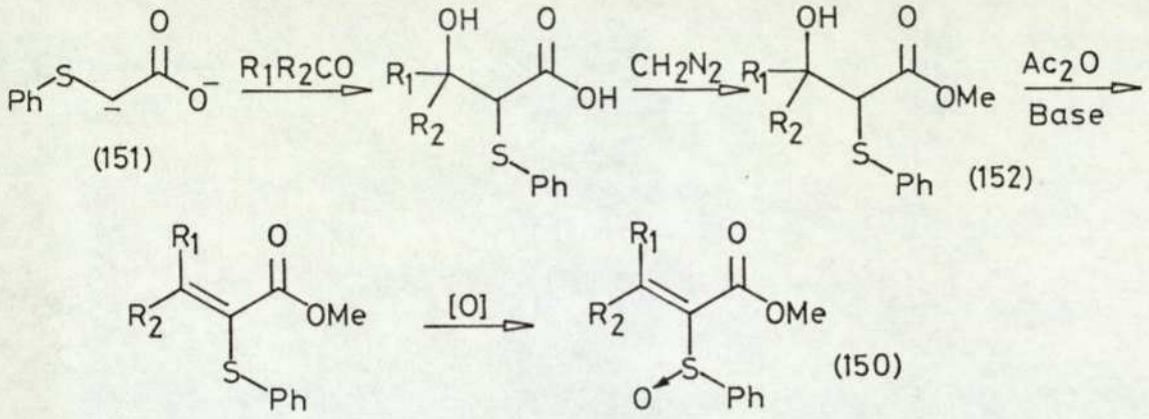


significant factor. Unlike the reaction of simple sulphoxides, the initially formed ylid (147) is stabilised by the acetyl (R = Me) or the carbomethoxy (R = OMe) group. The acyl-stabilised sulphonium ylids are known to be acetylated on oxygen whilst the carboalkoxy-stabilised ones react more slowly on carbon.[91] Extending this analogy to our case, the ylid derived from PSA (147, R = Me) would be silylated further much more readily than the one obtained from MPSA (147, R = OMe). The presumed bis-trimethylsilyl derivative (148) can then eliminate the ether and add the chloride ion, either synchronously or via the sulphonium ion (149).

This reaction was not pursued any further, but it led to an investigation of the effect of Lewis acids on the enolate of MPSA. The impetus was provided by the current interest in the chemistry of vinyl sulphoxides and, more specifically, by the considerable synthetic potential of the, little known, conjugated ester sulphoxides (150).

Numerous methods have been used to prepare α,β-unsaturated sulphoxides involving elimination from β-substituted sulphoxides,[92] action of vinyl Grignards on sulphinic esters,[93] addition of organo-copper reagents to acetylenic sulphoxides,[94]

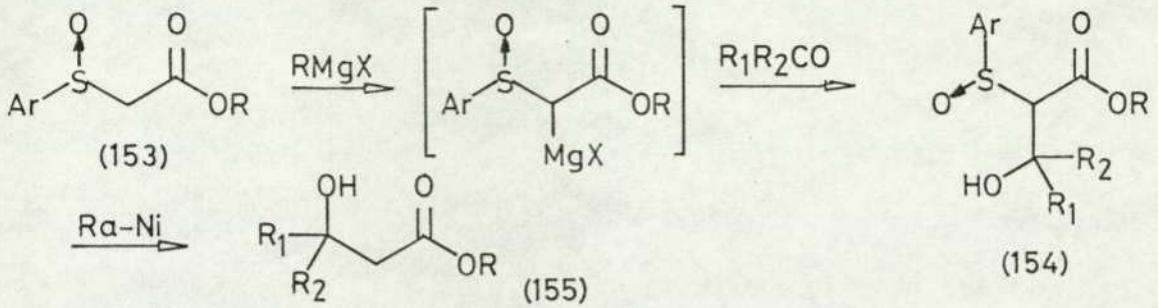
modified Wittig reaction[95] and trapping of sulphenic acids with acetylenes.[96] In contrast, only Uda's group has reported the synthesis of the unsaturated sulphoxide esters (150).[97,98] Their second,[98] more general method involved the reaction of the dianion of phenylthioacetic acid (151) with carbonyl compounds, followed by esterification,



dehydration and oxidation. Although the initial condensation and methylation were highly efficient, the dehydration had to be effected via acetylation and base-catalysed elimination of acetic acid. The latter steps were rather less successful and led to mixtures of geometric isomers. The acid-catalysed dehydration of the hydroxy esters (152) gave mixtures of α,β- and β,γ-unsaturated products depending on the nature of R_1 and R_2. Again, it seemed that the phenylsulphinyl group would provide the required degree of control resulting in a regiospecific reaction.

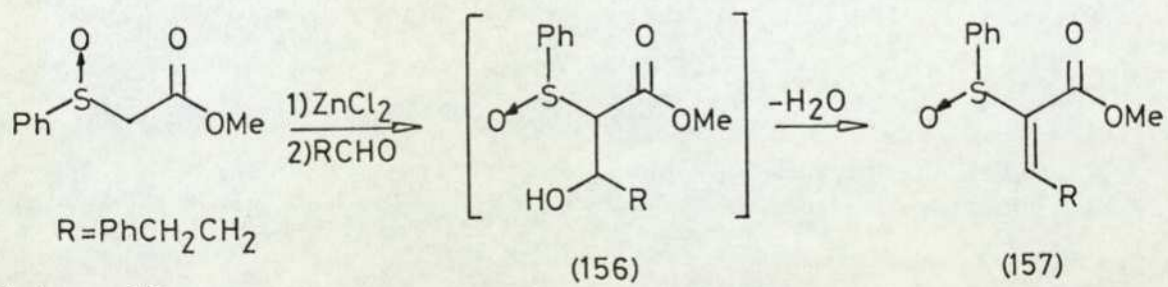
In principle, the condensations of MPSA with carbonyls should be amenable to the synthesis of compounds such as (150). Another Japanese group has found that a reagent derived from ethyl (phenylsulphinyl)acetate (153, R = Et) and ethyl magnesium bromide reacted with aldehydes and ketones

to give the hydroxy esters (154).[99] Sodium and lithium enolates did not react. Subsequently Mioskowski and Soladie



have reported that the reagent prepared from the optically active sulphinyl ester (153, Ar = p-Me(C_6H_4), R = t-Bu) and tert-butyl magnesium chloride gave high yields of the aldol products (154). Desulphurisation with aluminium amalgam gave optically active hydroxy esters (155) of high enantiomeric purity.[100]

An alternative method of generating a similar reagent from MPSA seemed to be the addition of zinc chloride to the sodium enolate (Scheme 20). Such treatment would, perhaps, result in a Reformatsky-type reagent, which would then react



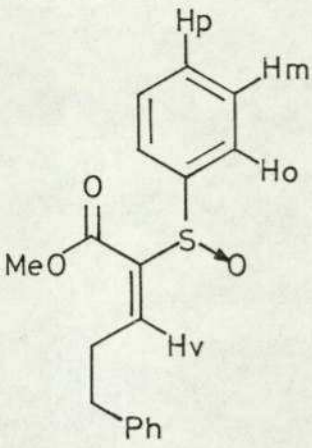
Scheme 20

with the carbonyl component to give the aldol adduct (156). Furthermore, the dehydrating properties of the Lewis acid might effect the elimination of water leading directly to the conjugated sulphoxide (157). Addition of anhydrous zinc chloride to the preformed sodium enolate of MPSA caused a

transient appearance of a milky precipitate, suggesting that the cation exchange did occur. After injection of 3-phenylpropionaldehyde (chosen to represent the aliphatic range) and stirring overnight at room temperature, t.l.c. analysis showed a single product, less polar than MPSA, in addition to the unconsumed starting materials. Refluxing the mixture caused the appearance of a bright-white precipitate and accelerated the rate of reaction. Preparative t.l.c. gave a compound whose i.r. spectrum showed strong absorptions at 1710, 1635 and 1045 cm^{-1}, indicating the presence of an α,β-unsaturated ester and a sulphoxide. The n.m.r. spectrum was undistinguished, exhibiting a methoxy singlet at δ3.68, a four-proton multiplet at δ2.8-3.3 and two aromatic multiplets totalling eleven protons. Irradiation in the aromatic region, and observation of the shape of the four-proton envelope, established the presence of an olefinic hydrogen, resonating at δ7.15. On this evidence the structure (157) was assigned. Since only one product could be detected, the relative geometry was not immediately obvious. However, the addition of a few crystals of $Eu(fod)_3$ caused a dramatic change in the aromatic region; other signals remained virtually unaffected. Four, well defined resonances were now observed, designated 1-4 in descending order of the magnitude of the induced shift (Figure 17).

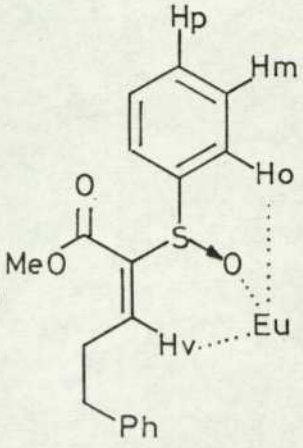
These results establish that the geometry about the double bond is as shown (i.e. E). Sulphoxides are known to be excellent chelating agents for the europium shift reagents.[101] The very large displacement observed for the

Figure 17



(157)

Observed	Induced
δ7.25 (Hv)	1. 1 H, m (Hv)
δ7.5-7.7 (Ho,Hm,Hp)	2. 2 H, m (Ho)
	3. 3 H, m (Hm,Hp)
δ7.3 (Ph)	4. 3 H, bs (Ph)

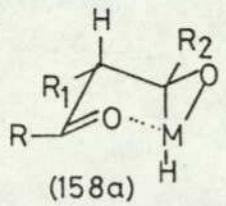


(157a)

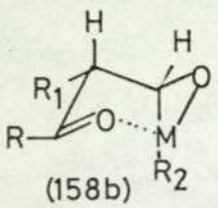
olefinic proton is indicative of its cis-relationship with the phenylsulphinyl group. The effect of europium complexes on the spectra of simple phenylsulphoxides parallels the observed trend, viz. the ortho-protons experience greatest deshielding.[102] The relative magnitudes of the induced shifts can be, perhaps, accounted for as depicted in (157a).

Thus the expectation that the zinc chloride-mediated reaction between MPSA and aldehydes would lead to the desired, conjugated sulphoxides was fully borne out. The mechanism of the formation of (156) is not clear, however. House and co-workers have investigated, in detail, the effect of zinc and magnesium halides on the aldol condensation of ketone enolates with aldehydes.[103] The lithium or sodium enolates were pre-treated with the Lewis acids in a manner similar to the procedure described above. As expected, the zinc or magnesium salts thus formed were found to stabilise the aldol products, and to influence the stereochemistry of the reaction. Where diastereoisomeric mixtures resulted the predominant products were those originating from the intermediate, six-membered, cyclic metal chelate in which the

greater number of substituents occupied the equatorial positions, i.e. (158a) was found more stable than (158b).



(158a)

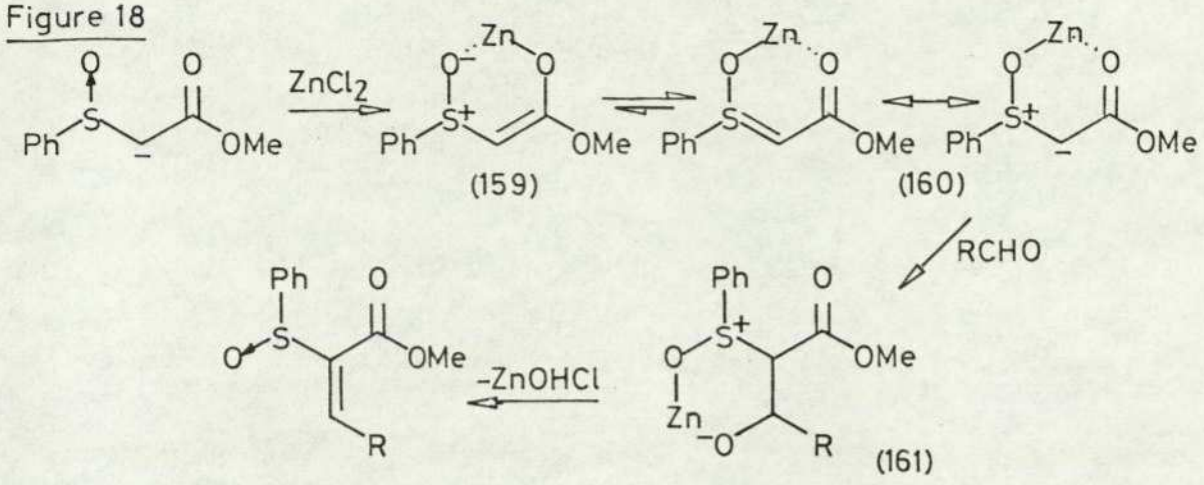


(158b)

The regiospecificity of the present reaction is presumably due to the preferential formation of a related complex. There are several reasons, however, for thinking that the reaction may not involve a straightforward Reformatsky-type process followed by dehydration. First, the aldol product (156) was not detected in the crude product. This may have been due to the prolonged reaction time; House et al. isolated their products after 5 minutes at ice-bath temperatures. That was not the case though. When the addition of 3-phenylpropionaldehyde was carried out at $0^{o}C$, the t.l.c. analysis of an aliquot, worked-up after 4 minutes, showed only the starting materials. Secondly, the reaction appears to be remarkably clean, on t.l.c. evidence. The American group[103] reported the usual aldol by-products, particularly prominent in an experiment which involved the zinc chloride-treated sodium enolate of phenylacetone and butyraldehyde (i.e. a system quite closely related to the case in hand).

These observations suggest that an alternative mechanism may be operating (Figure 18). The reactive species could be the ylid (160) rather than the enolate (159). This is a reasonable assumption in view of the greater basicity

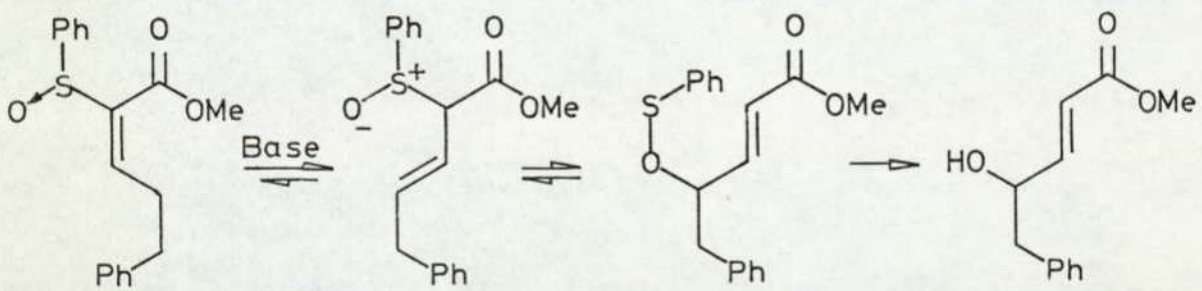
Figure 18



(and chelating power) of the sulphoxide oxygen relative to the ester. The reaction of the ylid with the aldehyde would give the betaine (161) whose formation would be controlled by the steric and electronic parameters. The subsequent elimination of basic zinc chloride, would lead to the observed product. Indirect support for this "ylid mechanism" comes from the observation that, both, acetophenone and benzylideneacetone failed to react under identical conditions. This is consistent with the known low reactivity of stabilised sulphur ylids,[104] and in contrast to the behaviour of the, previously discussed, "Grignard reagents". It is interesting to note that seemingly small alterations in the method of preparation and the nature of the cation appear to have a profound effect on the type and the reactivity of the species produced.

The general technique of treating an alkali metal enolate of an α-sulphinyl carbonyl compound with Lewis acids, or perhaps transition metal complexes, may serve to produce highly selective reagents. This aspect of sulphoxide chemistry could form the basis of a substantial future study.

Although the generality of the novel synthesis, just described, has not been established, the reaction with aldehydes should provide a good entry into the synthetically valuable α-sulphinyl-α,β-unsaturated esters. One interesting feature of such systems is the opposite effect of the ester and the sulphoxide substituents on the position of the double bond. It has been established that β,γ-unsaturated sulphoxides are thermodynamically more stable than the α,β-isomers.[105] The reverse is true for unsaturated esters. It was anticipated therefore that in the presence of a base equilibration should occur (Scheme 21). In turn, the resultant allylic sulphoxide (162) would be in equilibrium with the sulphenic ester (163).[106] Evans has shown that in the presence of thiophiles this equilibration can be utilised to prepare allylic alcohols.[107]



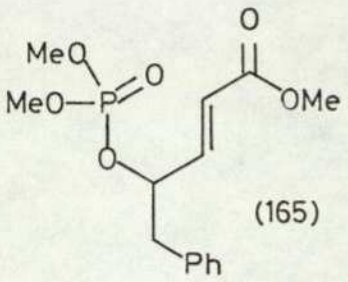
(162) (163) (164)

Scheme 21

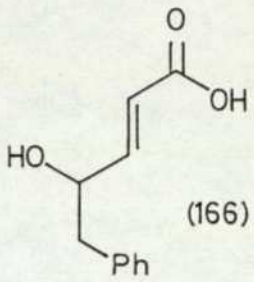
In the present case an additional driving force for this rearrangement would be provided by the tendency of the β,γ-unsaturated ester (162) to equilibrate with the conjugated isomer (163).

As anticipated, the sulphoxide (157) reacted smoothly in the presence of triethylamine and trimethyl phosphite. Somewhat unexpectedly two products were obtained. The less

polar material was the expected hydroxy ester (164). The more polar, minor product appeared to be the phosphate ester (165). Although this compound was not obtained analytically pure, the presence of strong absorptions at 1270 and 1040 cm^{-1} in its i.r. spectrum and of a six-proton triplet



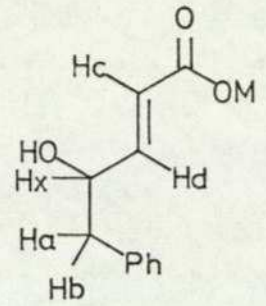
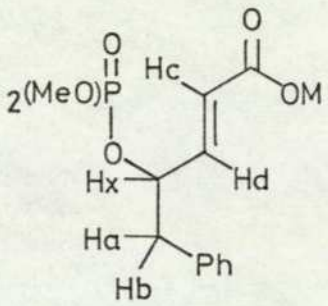
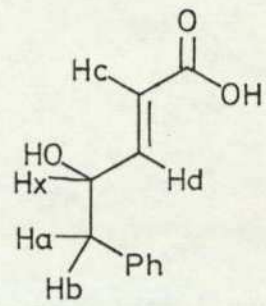
(165)



(166)

(J = 12 Hz) in the n.m.r. spectrum is good evidence for the proposed structure; the non-equivalence of the methyl groups is presumably due to the asymmetric centre. Furthermore, the presumed phosphate (165) was slowly hydrolysed by aqueous potassium hydroxide to give the hydroxy acid (166). Methylation of the latter substance gave material identical with the ester (164). The n.m.r. data for the three compounds is compiled in Table IV. The assignments were confirmed by decoupling experiments. Thus, in the case of (164), the irradiation of the multiplet at δ4.56 changed the signal at δ2.9 to an AB quartet, and the two olefinic resonances at δ6.08 and δ7.02 collapsed to sharp doublets (J = 16 Hz). A similar result was obtained with the phosphate (165) the sole difference being the collapse of the doublet at δ3.05 to a broad singlet. The unusually high chemical shift of the hydroxylic proton in (164) can be attributed to the deshielding effect of the phenyl group. The implication of a preferred conformation (164a) is corroborated by the

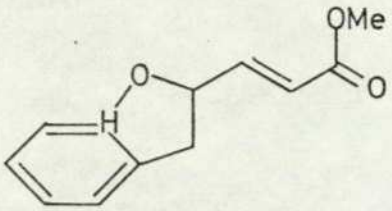
Table IV

			
Ha, Hb	2.9 m*	3.05 d J = 7 Hz	2.9 m
Hx	4.56 m	5.17 m	4.60 m
Hc	6.08 dd J = 16,2 Hz	6.05 dd J = 15.5,1 Hz	6.16 dd J = 16,1 Hz
Hd	7.02 dd J = 16,6 Hz	6.90 dd J = 15.5,7 Hz	7.20 dd J = 16,5 Hz
Ph	7.3 bs	7.3 bs	7.3 bs
CO_2Me	3.70 s	3.73 s	---
POMe	---	3.62 t J = 12 Hz	---
OH	2.0*	---	5.9
CO_2H	---	---	

* Dilution dependent, see text

clearly defined ABX pattern. As would be expected, this phenomenon was found to be dependent on dilution. In a

(164a)



more concentrated sample the hydroxylic proton moved downfield and the methylene signal became a broad doublet (J = 7 Hz).

It is apparent that the use of trimethyl phosphite as the thiophile[107] was not entirely satisfactory (cf. Chapter 2). This problem was also mentioned in a recent publication concerned with regiospecific γ-hydroxylation of α,β-unsaturated esters.[108] This transformation involved the analogous allylic sulphoxide-sulphenate rearrangement. The use of conventional thiophiles led to complications. Interestingly, satisfactory results were obtained by warming the sulphoxide in a phosphate buffer (pH 7). In the light of these findings trimethyl phosphite may well have been superfluous. In fact, the rearrangement occurs so readily that the sulphoxide (157) has to be stored in the cold. It appears to be catalysed by small amounts of impurities. The ester sulphoxide was initially obtained as an oil and analysed correctly as such. However, when left for a few days at room temperature it was found to decompose slowly to the hydroxy ester (164); subsequent chromatography gave the latter compound in approximately 10% yield. When stored for several weeks below $0^{o}C$ the purified oil deposited the crystalline

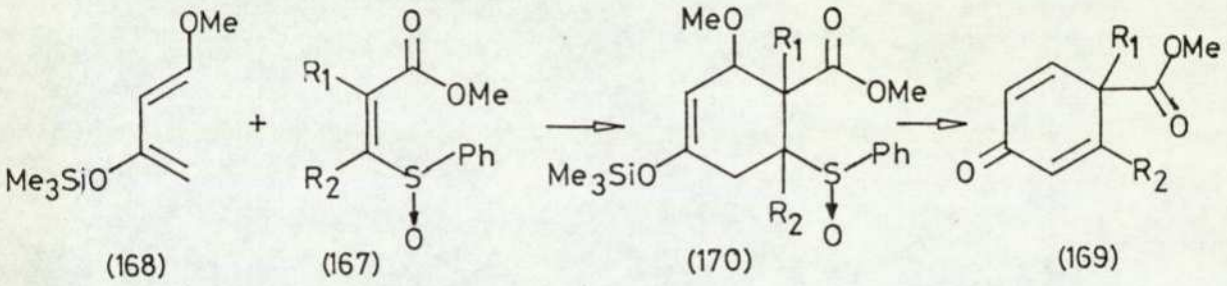
sulphoxide, and in that form the material was relatively more stable.

The γ-hydroxy-α,β-unsaturated ester functionality occurs widely in nature, e.g. cytochalasins A and B,[109] brefeldin A.[110] The novel, two-step transformation of an aldehyde (with α-hydrogens) into such a system, under very mild conditions, is a useful addition to the existing methodology.[108,111] An additional attraction of this method is the potential application to the synthesis of optically active compounds since the sulphoxide-sulphenate rearrangement is usually highly stereospecific.[107]

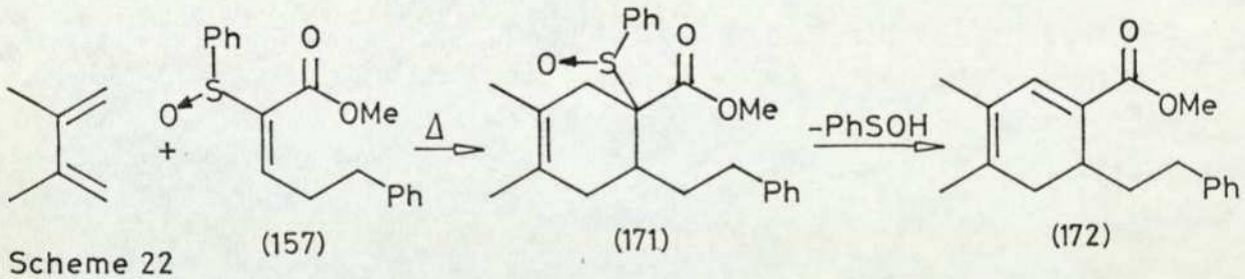
Asymmetric synthesis employing chiral, vinyl sulphoxides as Michael acceptors has been the subject of several publications.[112,113,114] The optical purity of the products is generally high. Particularly interesting is the work of Tsuchihashi[114] who not only managed to obtain optically active compounds, from p-tolyl styryl sulphoxide and carbon acids, but also found that subtle modifications in the nature of the solvent and the counter-ions caused the preferential formation of either epimer. Thus the two antipodes are available from the same starting material. The α-phenylsulphinyl - α,β-unsaturated esters have been shown to be good Michael acceptors by the Japanese workers.[99,115]

The variety of Pummerer-type rearrangements of methyl (α-phenylsulphinyl) cyclopentylideneacetate (see Review) is a further illustration of the range of reactions possible with this class of compounds.

Another potential, as yet untried, application of the ester sulphoxide (157) seemed to be as a dienophile. Simple vinyl sulphoxides are known to undergo Diels-Alder reactions.[116,117] Danishefsky and co-workers have reported that the β-phenylsulphinyl-α,β-unsaturated carbonyls (167) react readily with the highly oxygenated diene (168) to give the dienones (169), or phenols when R_1 = H. The presumed intermediate (170) could not be isolated.[118] Consequently



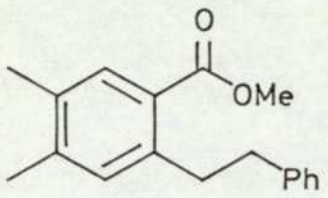
the reaction of (157) with dienes appeared highly promising (Scheme 22). An intriguing possibility here was that, with acyclic dienes, the cyclohexene intermediate (171) should



Scheme 22

eliminate phenylsulphenic acid regiospecifically to give the conjugated cyclohexadiene (172). The reaction of (157) with 2,3-dimethyl butadiene fulfilled these expectations. Refluxing the neat mixture overnight gave rise to two products. The prominent n.m.r. features of the more polar, major product were a broad, one-proton singlet at δ6.96, a methoxy singlet at δ3.76 and a broad, six-proton signal at δ1.80. This

compound was subsequently fully characterised as the dienoic ester (172). The less polar material showed two one-proton singlets at δ7.05 and δ7.75, a broad phenyl singlet at δ7.3, a methoxy resonance at δ3.92, two broad two-proton triplets at δ2.9 and δ3.1 and two broad singlets at δ2.42 and δ2.46 totalling six protons. On this evidence the fully aromatic structure (173) can be confidently accepted.



(173)

When the reaction was repeated in a sealed tube, which was kept at 80° during two days, the formation of (173) was completely suppressed. The dienoic ester (172) and benzenephenylthiosulphinate were the only products. The reaction appeared to be virtually quantitative, on t.l.c. evidence. Preparative t.l.c. gave a 60% yield of an analytically pure, colourless oil whose u.v. spectrum showed λ_{max} 313 nm; the calculated value is 309 nm.

The presumed cyclohexene intermediate (171) is clearly unstable at this temperature, in agreement with the findings of Danishefsky's group.[118] An attempt to isolate the intermediate by conducting the reaction at room temperature was unsuccessful. Although a polar product (R_f value similar to the starting sulphoxide) could be detected, the rate of conversion was too slow to be of practical significance, and even at this temperature the diene (172) was seen to have formed.

The overall reaction is a useful addition to the, already formidable, range of Diels-Alder reactions, particularly in view of the regiospecificity of the sulphoxide fragmentation. Although compounds such as (157) can be regarded as acetylenic ester equivalents their reaction with acyclic dienes is seen to furnish products not available from the alkynyl compounds. Quite apart from this obvious structural difference, acetylenic esters carrying an alkyl substituent are not very good dienophiles. In cyclo-additions of (157) to unsymmetrical dienes the sulphoxide would be expected to reinforce the directing influence of the carbomethoxy group giving regiospecific reactions. Given the wide range of dienes currently available, and the ready preparation of the conjugated ester sulphoxides, the scope for the investigation of the dienophilic properties of this family of compounds is virtually unlimited.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin-Elmer 157G spectrometer. Solids were analysed as nujol mulls, oils as thin films between sodium chloride plates. Frequencies of maximum absorptions (ν_{max}) are quoted in wavenumbers (cm^{-1}). Ultraviolet spectra were recorded, for ethanolic solutions, on a Unicam SP800 instrument, λ_{max} values are given in nanometers. Proton n.m.r. analyses were performed on a Jeol MH100 spectrometer for deuteriochloroform solutions, except where stated otherwise, with tetramethylsilane as internal reference. Chemical shifts are quoted in δ values, coupling constants in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = complex multiplet, b = broad, exch. = disappears on addition of D_2O. The values of complex resonances are given as a range, e.g. δ7.2-7.5 (5 H, m), except where the multiplet had an analysable pattern. In these cases the chemical shift is given as the centre of the signal. Mass spectra were obtained on an AEI MS30 instrument.

All solvents were GPR grade and were distilled before use except for dichloromethane and chloroform. Ether and benzene were dried over sodium. Tetrahydrofuran (THF) was distilled from lithium aluminium hydride. Anhydrous methanol was obtained by distillation from magnesium methoxide. Petrol refers to petroleum ether boiling in the range 40-60°.

Merck silica gel GF_{254} was used for both preparative

and analytical t.l.c.

Organic extracts were dried over anhydrous magnesium or sodium sulphate. Solvents were removed *in vacuo* on a Büchi rotary evaporator. Reactions were routinely carried out under positive pressure of dry nitrogen or argon.

3-acetyl-4-hydroxy-6-methyl-pyran-2-one (Dehydroacetic acid) (12)

The method described in Org. Syn. Coll. Vol., III, p.231-3 was followed.

Ethyl acetoacetate (65 g, 0.5 M) was heated with powdered sodium hydrogen carbonate (30 mg) at 205° for 5½ h with continuous removal of ethanol. The resultant deep-red oil was distilled at 12 mm Hg collecting the fraction boiling in the range 130-145°; the fore-run consisted of ethyl acetoacetate (24.6 g, 38%). Crystallisation of the solidified product from ethanol gave dehydroacetic acid (11.37 g, 37%), m.p. 108-9° (lit. m.p. 108°), ν_{max} 1720, 1630, 1550 cm^{-1}, δ2.26 (3 H, s), 2.64 (3 H, s), 5.58 (1 H, s), 16.48 (1 H, s, exch.).

3-acetyl-4-hydroxy-6-pentyl-pyran-2-one (22)

Sodium metal (0.42 g, 0.018 M) was added, in small pieces, to liquid ammonia (150 ml) containing a few crystals of ferric nitrate. To the stirred, grey suspension of sodium amide thus formed dehydroacetic acid (0.84 g, 0.005 M) was added portion-wise. The resultant yellow-brown suspension was stirred for a further 2 h and n-butyl bromide (0.81 g, 6 mM) added dropwise in anhydrous ether (150 ml). The mixture was stirred for 1 h, quenched with ammonium chloride (1.6 g) and diluted with ether (150 ml). After the removal of ammonia and addition of water the cold mixture was neutralised with conc. HCl. The dried organic phase was evaporated to give the title pyranone (1.17 g, 52%) as an

orange oil which solidified on standing. Crystallisation from aqueous ethanol gave a waxy, white solid m.p. 35-38°, ν_{max} 1720, 1630, 1550 cm^{-1}, δ0.9 (3 H, m), 1.24-1.48 (4 H, m), 1.50-1.80 (2 H, m), 2.52 (2 H, t, J = 7 Hz), 2.68 (3 H, s), 5.97 (1 H, s), 16.56 (1 H, s, exch.), (Found: M^+ 224.1060; $C_{12}H_{16}O_4$ requires 224.1049).

3-acetyl-4-hydroxy-6-(5-hexenyl)-pyran-2-one (23)

The trianion of dehydroacetic acid (0.84 g, 0.005 M) was generated, as in the previous experiment, using sodamide (0.021 M). Alkylation with 5-bromo-1-pentene gave a red oil (0.98 g). A portion (284 mg) was chromatographed on silica eluting with toluene/acetone/acetic acid (94:5:1) giving a yellow oil (136 mg, 40%) which contained the title compound together with some di-alkylated material. Further chromatography (toluene/acetic acid - 99:1) of 120 mg of the purified mixture gave the title pyranone (75 mg) as an oil which deposited long needles m.p. 35°, ν_{max} 1730, 1640 (1630 sh), 1550 cm^{-1}, δ1.3-1.8 (4 H, m), 2.10 (2 H, m), 2.52 (2 H, bt, J = 8 Hz), 2.68 (3 H, s), 5.00 (1 H, bd, J = 10 Hz), 5.03 (1 H, bd, J = 16 Hz), 5.80 (1 H, m), 5.96 (1 H, s), 16.65 (1 H, bs, exch.), M.S. 236 (2), 168 (35), 153 (61), 111 (28), 98 (27), 69 (39), 43 (100), (Found: M^+ 236.1053; $C_{13}H_{16}O_4$ requires 236.1049).

The less polar compound (30 mg) was the di-alkylated material 3-acetyl-4-hydroxy-6-(undeca-1,10-dien-6-yl)-pyran-2-one, an oil, δ1.3-1.8 (8 H, m), 1.9-2.2 (4 H, m), 2.5 (1 H, m), 2.70 (3 H, s), 5.0 (2 H, bd, J = 10 Hz), 5.04

(2 H, bd, J = 16 Hz), 5.8 (2 H, m), 5.94 (1 H, s), 16.6 (1 H, bs, exch.).

4-hydroxy-6-methyl-pyran-2-one (Triacetic lactone) (20, R = H)

Dehydroacetic acid (4.20 g, 0.025 M) was dissolved in 90% sulphuric acid (12.6 g) [obtained from conc. H_2SO_4/water - 17: 2] and warmed at 130° until no starting material remained (ca. 10 min). This was monitored by allowing a droplet of the reaction mixture to fall into cold water; when no precipitate could be seen the reaction was complete. The reaction mixture was poured into ice-water (16 ml) and cooled in an ice-bath. The yellow solid thus obtained was recrystallised from water to give the title lactone (2.12 g, 77%), as buff needles, m.p. 184-186° (lit.[119] m.p. 188-189°, lit.[120] m.p. 186-186.5°).

Triacetic lactone (1.26 g, 10 mM), dimethyl sulphate (1.1 ml) and anhydrous, powdered potassium carbonate (1.5 g) were refluxed in dry acetone (10 ml) until the starting material could no longer be seen (ca. 5 h). The mixture was stirred overnight, filtered and evaporated to give 4-methoxy-6-methyl-pyran-2-one (20, R = Me) (1.36 g, 97%) as a yellow solid. Crystallisation from petrol gave pale-yellow crystals m.p. 84-87° (lit.[121] m.p. 87-88°), δ2.20 (3 H, s), 3.78 (3 H, s), 5.38 (1 H, d, J = 2 Hz), 5.76 (1 H, bs).

Ethyl 5-phenyl-5-hydroxy-3-oxo-hexanoate (31)

Ethyl acetoacetate (1.30 g, 10 mM) in THF (5 ml) was

added to the stirred suspension of sodium hydride (55%, 0.48 g, 11 mM) in THF (20 ml) at 0^{o}. The greyish solution was stirred at that temperature until hydrogen evolution ceased (ca. 25 min) and n-butyl-lithium (6 ml, 11.5 mM) added over 10 min. The orange solution was stirred for a further 15 min and acetophenone (1.37 g, 11.4 mM) added rapidly in THF (5 ml). The orange colour was immediately discharged. The yellow solution was stirred for a further ½ h, attaining room temperature and quenched with ether (15 ml), water (5 ml) and conc. HCl (3 ml). The layers were separated and the aqueous phase extracted with ether (3 x 10 ml). The combined organic layer was washed with water, until neutral and brine. Evaporation of the dried solution yielded an orange oil (2.89 g). Chromatography (dichloromethane/methanol - 99.5:0.5) of 274 mg of the crude product gave the essentially pure compound (190 mg, 78%). Further chromatography (petrol/ethylacetate - 90:10) gave the, analytically pure, title aldol (135 mg), as an oil, ν_{max} 3500, 1730, 1705, 1315, 1260, 1160, 1030, 765, 700, δ1.20 (3 H, t, J = 7 Hz), 1.52 (3 H, s), 2.96 and 3.24 (2 H, ABq, J = 16 Hz), 3.35 (2 H, s), ∿3.9 (1 H, bs, exch.), 4.12 (2 H, q, J = 7 Hz), 7.2-7.5 (5 H, m); peaks due to the enolic form (∿13%) at δ2.68, 4.86 and 12.2, (Found: C, 67.13, H, 7.29. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.24).

Reaction of the aldol (31) with p-toluenesulphonic acid

The crude aldol (31) (954 mg, ∿80%, 3.05 mM) was refluxed in benzene (100 ml) in the presence of p-toluene-sulphonic acid (0.45 g) with continuous removal of water.

After 5 h the orange solution was cooled and concentrated. This resulted in precipitation of a white solid. Crystallisation from benzene gave the lactone of 5-phenyl-5-hydroxy-3-oxo-hexanoic acid (33), (398 mg, 63%), as white crystals, m.p. 106-110°, ν_{max} 3180 (enol), 1670, 1620, 1250, 835, 770, 700, δ1.76 (3 H, s), 2.91 and 3.23 (2 H, ABq, J = 20 Hz), 2.89 and 3.37 (2 H, ABq, J = 16 Hz), 7.34 (5 H, s), (Found: C, 70.56; H, 5.86. $C_{12}H_{12}O_3$ requires C, 70.58; H, 5.92). A portion (43 mg) of the mother liquor (460 mg) was chromatographed (dichloromethane/petrol - 75:25) to give 19 mg of the, subsequently identified, impure olefin (32) (estimated yield - 12%).

Reaction of the aldol (31) with ethyl chloroformate

Crude aldol (31) (156 mg) in THF (3 ml) was added dropwise to the stirred suspension of sodium hydride (55%, 90 mg) in THF (10 ml). The initially pale-yellow colour of the aldol solution intensified as the addition progressed. After ½ h at 0° ethyl chloroformate (106 mg) in THF (2 ml) was injected. There was an immediate colour discharge. An aliquot was worked-up by tossing into dil. HCl and ether. The organic phase was washed with water and dried. The product was unstable on silica; the n.m.r. spectrum established its identity as the enol carbonate (38), a colourless oil, δ1.2 (6 H, m), 1.60 (3 H, s), 2.75 and 3.01 (2 H, ABq, J = 14 Hz), 4.10 (4 H, dq, J = 7 Hz), 5.58 (1 H, s), 7.2-7.5 (5 H, m) and one exchangeable proton at δ2.8.

The reaction mixture was stirred for a further 5 h and

then refluxed overnight. A complex mixture resulted (n.m.r.) although some olefin (32) appeared to have formed (t.l.c.).

Reaction of the aldol (31) with phosgene

Crude aldol (31) (80%, 286 mg, 0.92 mM) was dissolved in anhydrous toluene (2 ml) containing pyridine (0.25 ml, 2.75 mM). A 12.5% solution of phosgene in toluene (1 ml, 1.26 mM) was added at 0^{o} resulting in an instantaneous formation of a white precipitate. The mixture was stirred for a further 1 h and quenched with water (10 ml) and ether (10 ml). The aqueous layer was extracted with ether (2 x 5 ml) and the combined organic phase washed with water and dried. Evaporation of the solvent gave a red oil (247 mg). Chromatography (petrol/ether - 85:15) of a portion (139 mg) of the crude product gave a mixture of the olefins (32a), (32b) and (32c). The n.m.r. data is given in the text (Fig. 4).

Ethyl 5-phenyl-5-acetoxy-3-oxo-hexanoate (40)

Crude aldol (31) (440 mg, 80%, 1.4 mM) was dissolved in acetic anhydride (5 ml). Pyridine (0.6 ml) was added and the solution stirred overnight. Saturated, aqueous sodium hydrogen carbonate (10 ml) was added to the cooled (0^{o}) solution and the resulting mixture stirred vigorously at room temperature (3 h). Ether was added and the aqueous phase acidified (conc. HCl) and extracted with further portions of ether. The combined, washed (water) and dried organic layer on evaporation yielded a yellow oil (484 mg). A portion (69 mg) of the crude product was chromatographed

(petrol/ether - 85:15) to give the title compound (46 mg, 80%), as a faintly yellow oil, ν_{max} 3500 (w, enol), 1735, 1650, 1235, 760, 700, δ1.25 (3 H, t, J = 7 Hz), 1.94 (3 H, s), 2.10 (3 H, s), 3.30 (2 H, s), 3.34 and 3.46 (2 H, ABq, J = 16 Hz), 4.20 (2 H, q, J = 7 Hz), 7.40 (5 H, bs); peaks due to the enolic form (∿10%) at δ3.70, 4.92 and 12.10. Further chromatography (petrol/ethyl acetate - 98:2 rising to 95:5) gave the analytically pure sample (Found: C, 65.57; H, 6.92. $C_{16}H_{20}O_5$ requires C, 65.75; H, 6.89).

Ethyl (4-E)-5-phenyl-3-oxo-hex-4-enoate (32a) and ethyl (4-Z)-5-phenyl-3-oxo-hex-4-enoate (32b)

Crude acetate (40) (67%, 400 mg, 0.91 mM) was dissolved in aqueous ethanol (50%, 30 ml), saturated, aqueous sodium hydrogen carbonate (5 ml) added and the solution stirred for 2 days at room temperature. Ether (25 ml) and dil. HCl (10 ml) was added, the layers separated and the aqueous phase extracted with further portions of ether (3 x 20 ml). The combined organic phase was washed with water, till neutral, brine, dried and evaporated to give a yellow oil (287 mg). Chromatography (petrol/ether - 90:10) of the crude product yielded the olefin (32a) contaminated with traces of the olefin (32b), (179 mg, 83%), as a pale-yellow oil, (Found: C, 72.55; H, 6.90. $C_{14}H_{16}O_3$ requires C, 72.37; H, 6.94). Multiple elution (petrol/ether - 95:5) effected the separation of the two isomers: (32a), ν_{max} 1740, 1685, 1600, 1240, 1155, 760, 700 cm^{-1}, δ1.30 (3 H, t, J = 7 Hz), 2.60 (3 H, bs), 3.60 (2 H, s), 4.24 (2 H, q, J = 7 Hz), 6.63 (1 H, bs),

7.4-7.6 (5 H, m), peaks due to the enolic form at δ2.28, 5.16, 6.08, 12.42, (32b), ν_{max} 1740, 1690, 1600, 1240, 1155, 765, 700 cm^{-1}, δ1.22 (3 H, t, J = 7 Hz), 2.22 (3 H, bs), 3.18 (2 H, s), 4.13 (2 H, q, J = 7 Hz), 6.27 (1 H, bs), 7.2-7.6 (5 H, m), peaks due to the enolic form at δ1.76, 4.87, 5.90, 11.90.

Condensation of the dianion of ethyl acetoacetate with acetophenone followed by quenching with acetic anhydride

The dianion of ethyl acetoacetate (1.294 g, 9.9 mM) was generated as described previously. Acetophenone (1.293 g, 10.75 mM) was added rapidly in a small volume of THF and the pale-yellow solution stirred for 15 min. The reaction was quenched with acetic anhydride (5 ml) when an immediate formation of a white precipitate was observed. After 1 h, ether (20 ml) and water (10 ml) were added and the two phases shaken with solid sodium hydrogen carbonate until effervescence ceased. The mixture was neutralised (conc. HCl) and the layers separated. The aqueous phase was extracted with further portions of ether. The combined organic layer was processed in the usual way to yield a yellow oil (3.394 g), which was a mixture of three major products. A portion (50 mg) of the crude products was chromatographed (petrol/ether - 90:10) to give two fractions. The more polar material (13 mg, 31%) was a solid which was recrystallised from petrol to give 5-phenyl-2,5-dimethyl-3-carbethoxy-5,6-dihydro-pyran-4-one (41), m.p. 85-86°, ν_{max} 1700, 1670, 1550, 1210, 1090, 765, 700 cm^{-1}, δ1.26 (3 H, t, J = 7 Hz), 1.68 (3 H, s), 2.27

(3 H, s), 2.83 and 3.04 (2 H, ABq, J = 16 Hz), 4.18 (2 H, q, J = 7 Hz), 7.26 (5 H, s), (Found: C, 70.13; H, 6.75. $C_{16}H_{18}O_4$ requires C, 70.08; H, 6.61). The less polar fraction (16.6 mg) was a mixture of the acetate (40) and the acetyl-acetate (42). The yields, estimated from the n.m.r. integral were 21% and 15% respectively. The acetate (42) showed characteristic peaks at δ2.28 (3 H, s) and 17.6 (3/4 H, s, exch.); the other signals were obscured by the peaks due to the mono-acetate (40). Treatment of this mixture with aqueous, ethanolic sodium hydrogen carbonate gave, after 30 h, the dihydropyrone (41) and the olefin (32) (t.l.c.).

The remaining, original, crude mixture was dissolved in aqueous ethanol (50%, 100 ml) and stirred with saturated, aqueous sodium hydrogen carbonate (15 ml) for 3 days. The mixture was worked-up, as described in the preceding experiment, to give an oil (2.954 g) which was chromatographed (petrol/ether - 90:10) to give the olefin (32) [283 mg, 12%:11% of (32a) and 1% of (32b)] and the dihydropyrone (41) (1.090 g, 40%).

Attempts to aromatise the olefin (32)

Thermolysis of the olefin in refluxing benzene and toluene (24 h) led to the recovery of the starting material. Heating the olefin in refluxing mesitylene (2 days) gave a less polar yellow oil, identified as the mixture of (E) and (Z) 4-phenyl-pent-3-en-2-one (45), a yellow oil (12 mg, 64%), ν_{max} 1680, 1600, 760, 695 cm^{-1}, δ2.28 (9 H, bs), 2.52 (3 H, s),

6.48 (1 H, bs), 6.80 (1 H, bs), 7.2-7.5 (10 H, m).

The olefin was inert in the presence of excess of sodium hydride in benzene at room temperature. In refluxing benzene and toluene the starting material decomposed slowly to intractable polar tar.

The olefin (32a) (28 mg, 0.12 mM) in THF (2 ml) was added to the stirred suspension of sodium hydride (55%, 7 mg, 0.16 mM) in THF (2 ml) at 0^{o}. After 15 min n-butyl-lithium (1.9 M, 0.08 ml, 0.15 mM) was added to the yellow solution. The reaction mixture became orange. After stirring overnight at room temperature the flask was immersed in a bath (60^{o}) and held there for 5 h. Addition of water and conc. HCl caused the red-orange colour of the cooled reaction mixture to become pale-yellow. The usual extraction gave 35 mg of an orange oil which was chromatographed (petrol/ether - 92.5:7.5) to give the starting olefin (32a) (1.3 mg, 4.7%) and the deconjugated isomer (32c) (1.6 mg, 5.8%).

The above reaction was repeated with the olefin (32a) (97 mg, 0.42 mM), sodium hydride (55%, 53 mg, 1.2 mM) and n-butyl-lithium (0.5 ml, 0.9 mM). Total volume of THF was 10 ml. After stirring the dark-brown mixture overnight it was quenched with heavy water (3 ml) when the brown colour became yellow. The mixture was diluted with ether and processed in the usual way to yield an orange oil (119 mg), which contained traces of the starting material, the deconjugated olefin (32c) and polar tar (t.l.c.). The n.m.r. integral of the peak at δ3.44, as compared to the terminal olefin signals, was 1¼ H which corresponds to 75% incorpor-

ation of deuterium at the 4-position.

The same reaction was repeated using HMPA as the solvent. The olefin (32) (29 mg, 0.13 mM) was added to sodium hydride (55%, 13 mg, 0.3 mM) followed by n-butyl-lithium (0.1 ml, 0.16 mM). A dark-brown solution was obtained which was stirred overnight and then heated at 80° for 2 h. The cooled solution was treated with an excess of methyl iodide (1 ml) and after 15 min the reaction was worked-up in the usual way. Evaporation of the ethereal solution gave a yellow oil (29 mg) which was essentially the bis-methylated olefin (46) (71% calculated yield). Chromatography (petrol/ether - 98:2 rising to 95:5) gave the major product, ethyl (4E) 5-phenyl-3-oxo-2,2-dimethyl-hex-4-enoate (46a), as a faint-yellow oil, ν_{max} 1730, 1690, 1600, 1260, 1140, 760, 695 cm^{-1}, δ1.23 (3 H, t, J = 7 Hz), 1.43 (6 H, s), 2.58 (3 H, s), 4.23 (2 H, q, J = 7 Hz), 6.58 (1 H, bs), 7.46 (5 H, bs), (Found: M^+ 260.1418. $C_{16}H_{20}O_3$ requires 260.1412), and the more polar, minor product, ethyl (4Z) 5-phenyl-3-oxo-2,2-dimethyl-hex-4-enoate (46b), as an oil, ν_{max} 1730, 1690, 1620, 1260, 1140, 765, 700 cm^{-1}, δ1.28 (3 H, t, J = 7 Hz), 1.37 (6 H, s), 2.20 (3 H, bs), 4.26 (2 H, q, J = 7 Hz), 6.32 (1 H, bs), 7.2-7.5 (5 H, m), (Found: M^+ 260.1416. $C_{16}H_{20}O_3$ requires 260.1412). The two olefins were obtained in a ratio (46a):(46b) = 10:1.

Quenching a THF solution containing the presumed dianion of the deconjugated olefin with trimethylsilyl chloride, followed by aqueous work-up gave the starting material, i.e. (32).

Treatment of the olefin (32a) (234 mg, 1 mM) with tri-

ethylamine (4 ml) and trimethylsilyl chloride (6 ml) in anhydrous benzene (20 ml), room temperature overnight, gave, after filtration, the mixture of trimethylsilyl enol ethers (47) contaminated with triethylammonium chloride (308 mg, estimated yield 95%), δ0.28 and 0.32 (18 H, 2 s), 1.24 (6 H, m), 2.30 (3 H, s), 2.38 (3 H, s), 4.1 (4 H, m), 5.16 (1 H, s), 5.24 (1 H, s), 6.1 (1 H, bs), 7.1-7.5 (11 H, m). Stirring the crude product with an excess of potassium t-butoxide in anhydrous benzene regenerated the starting olefin (32).

Ethyl 3-ethoxy crotonate (48)

Ethyl acetoacetate (13.0 g, 0.1 M) and ethyl ortho-formate (15.1 g, 0.102 M) were placed in a 50 ml Claisen flask, concentrated sulphuric acid (6 drops) was added and the mixture left to stand for 2 days. Quinoline (10 drops) was added and the mixture distilled at 12 mm Hg. The fraction boiling at 96-96.5° was collected as a solid (14.3 g, 90%), (lit.[41] b.p. 90-92°/15 mm), ν_{max} 1710, 1625, 1140, 1060, δ1.24 (6 H, dt, J = 7 Hz), 2.24 (3 H, s), 3.76 (2 H, q, J = 7 Hz), 4.04 (2 H, q, J = 7 Hz), 4.92 (1 H, s).

Acetylation of the crotonate (48)

Di-isopropylamine (0.30 ml, 2 mM) was dissolved in THF (2 ml) and n-butyl-lithium (0.8 ml, 2 mM) added dropwise at -78°. The colourless solution was allowed to warm to -50° and the crotonate (48) (294 mg, 1.86 mM) added dropwise in THF (3 ml). The yellow solution was warmed to 0°. The colour gradually became orange. Acetic anhydride (2 ml,

freshly distilled from quinoline) was added rapidly resulting in an immediate discharge of colour to pale-yellow. A heavy white precipitate was also observed. After stirring for a further 2 h at room temperature the mixture was diluted with ether and saturated, aqueous sodium hydrogen carbonate. After stirring overnight, the usual work-up afforded a yellow oil (311 mg), which was chromatographed (dichloromethane) to give the starting material (19 mg, 12%) and a more polar mixture of ethyl 2-acetyl-3-ethoxy crotonates (51a) and (51b), (95 mg, 27%) as an oil, ν_{max} 1710, 1680, 1620, 1200, 1080, δ1.2-1.4 (12 H, m), 2.16 (3 H, s), 2.32 (6 H, bs), 2.42 (3 H, s), 3.96-4.10 (8 H, m).

Phenylsulphinylacetone (PSA) (53)

Thiophenol (20 ml, 0.195 m) was added to the stirred solution of sodium hydroxide (9.5 g, 0.24 M) and benzyltriethylammonium chloride (5 g) in water (100 ml). The solution was cooled to 0^{o} and chloroacetone (freshly distilled b.p. 48-48.5^{o}/40 mm, 20 g, 0.22 M) added dropwise in dichloromethane (100 ml). After vigorous stirring overnight the layers were separated, the aqueous phase extracted with dichloromethane (3 x 50 ml) and the combined organic layer dried over sodium sulphate. Evaporation of the solvent gave phenylthioacetone as a yellow oil, which was distilled at 1.5 mm Hg collecting the fraction boiling at 110^{o} (lit.[122] b.p. 135-137^{o}/12 mm). The pale-yellow oil (25.56 g, 79%) solidified on standing, m.p. 32-35^{o}, ν_{max} 1710, 740, 690, δ2.22 (3 H, s), 3.66 (2 H, s), 7.2-7.4 (5 H, m).

Phenylthioacetone (16.6 g, 0.1 M) was dissolved in methanol (50 ml) and sodium metaperiodate (21.40 g, 0.1 M) in water (20 ml) added rapidly, dropwise at 0^{o}. The mixture was homogenised with methanol (100-150 ml) and stirred overnight. The inorganic salts were filtered and the cake washed well with methanol. The filtrate was reduced in volume until an oil separated. The mixture was extracted with dichloromethane (∿200 ml, total volume) and the organic layer dried over sodium sulphate, and evaporated to give phenylsulphinylacetone (17.14 g, 94%) as a yellow solid. Crystallisation from benzene/petrol gave the pure product, faintly yellow crystals, m.p. 74-76^{o} (lit.[123] m.p. 76-77^{o}), ν_{max} 1710, 1040, 750, 690 cm^{-1}, δ2.24 (3 H, s), 3.86 (2 H, bs), 7.3-7.7 (5 H, m).

Methyl (phenylsulphinyl)acetate MPSA (56)

The procedure followed above was used. Methyl (phenylthio)acetate, an oil, ν_{max} 1735, 1280, 1150, 740, 690, δ3.70 (2 H, s), 3.76 (3 H, s), 7.2-7.5 (5 H, m) was obtained in 77% yield from thiophenol and methyl chloroacetate. Oxidation with sodium metaperiodate gave the title sulphoxide in 98% yield. Crystallisation from ether gave colourless, chunky crystals, m.p. 48-50^{o}, (lit.[48] m.p. 45-48^{o}), ν_{max} 1740, 1295, 1170, 1040, 750, 700 cm^{-1}, δ3.75 (3 H, s), 3.78 (2 H, ABq, J = 14 Hz).

Reaction of PSA with methyl crotonate

PSA (183 mg, 1 mM) in THF (2 ml) was added dropwise to

the stirred suspension of sodium hydride (50 mg, ∿1 mM) in THF (3 ml) at 0^{o}. The clear solution was allowed to warm to room temperature during ½ h and methyl crotonate (100 mg, 1 mM) was added in THF (4 ml). The pale yellow solution was refluxed for 2 days. The brown reaction mixture was poured into ether and acidified (dil. HCl). The aqueous phase was further extracted with ether and the combined organic layer washed with water, till neutral, brine and dried. Evaporation of the solvent gave a dark-yellow oil (197 mg). The crude product was taken-up in ether and extracted with small portions of saturated, aqueous sodium hydrogen carbonate. The aqueous layer was made acid and extracted into ethyl acetate. The acidic fraction thus obtained (139 mg) contained mainly crotonic acid and PSA. The neutral (ether) fraction (35 mg) contained mainly orcinol (estimated yield ∿16%) and hydrocarbon impurities (t.l.c. and n.m.r.).

The analogous reaction of PSA with methyl cinnamate failed under all conditions tried, i.e. NaOMe/HOMe, $Mg(OMe)_2$/-HOMe, NaH/THF.

5-phenyl resorcinol (55, R = Ph)

Sodium metal (0.25 g, 10.4 mM) was dissolved in dry methanol (3 ml) and MPSA (1.98 g, 10 mM) added in methanol (1 ml). The orange-red solution was stirred for 1 h prior to the addition of benzylidene acetone (1.45 g, 10 mM) in methanol (1 ml). The red-brown solution was stirred overnight at room temperature. The reaction mixture was poured into water, acidified (conc. HCl) and extracted into ether.

The organic phase was washed and dried in the usual manner, and evaporated to give an orange oil (2.83 g). The crude product was triturated with ether giving a small amount of yellow powder and an oil which was treated with boiling water. Steam distillation gave white needles (130 mg), m.p. 55-57°, smelling faintly of thiophenol (diphenyl disulphide, m.p. 60.5°). Decantation of the residual water and cooling afforded 5-phenyl resorcinol (369 mg. 20%) as white crystals, m.p. 155-157°(lit.[124] m.p. 159°), δ(d_6-acetone) 6.38 (1 H, t, J = 2 Hz), 6.62 (2 H, d, J = 2 Hz), 7.3-7.6 (5 H, m), 8.5 (2 H, bs, exch.). The yellow powder, which showed broad peaks in the n.m.r. spectrum was subsequently identified as the cyclohexanedione intermediate (58).

A better result was obtained using an excess of magnesium methoxide in anhydrous methanol. Thus, dry magnesium turnings (100 mg, 4 mM) were dissolved in anhydrous methanol (4 ml). MPSA (198 mg, 1 mM) in methanol (4 ml) was added to the still warm solution. After 1 h benzylidene acetone (146 mg, 1 mM) in methanol (4 ml) was added and the yellow solution refluxed for a further 7 h. The cooled mixture was diluted with ether (30 ml) and washed with water (3 x 5 ml). The aqueous, alkaline phase thus obtained was acidified (dil. HCl) and extracted into ethyl acetate (4 x 10 ml). The neutral (ether) fraction gave a yellow oil (84 mg); the acidic fraction (ethyl acetate) yielded a brown solid (192 mg). Since both fractions contained the resorcinol they were combined and chromatographed (chloroform/ethyl acetate - 80:20) to give: MPSA (35 mg, 19%), 5-phenyl resorcinol (80 mg, 46%) and the

intermediate (58) (15 mg, 5%). The non-polar material contained mainly unreacted benzylidene acetone and diphenyl disulphide (n.m.r.).

Isolation of 5-phenyl-4-phenylsulphinyl-cyclohexane-1,3-dione (58). (General Method A)

A procedure similar to that described above was followed except that 8 equivalents of magnesium methoxide were used and the reaction mixture was stirred for 3 days at room temperature (1 mM scale). Methanol was then removed in vacuo and the orange syrup partitioned between ether and dil HCl. The ethereal layer was extracted with saturated, aqueous sodium hydrogen carbonate, washed with water and dried. The combined, aqueous, alkaline phase was acidified (conc. HCl) and extracted with ethyl acetate. The neutral fraction (43 mg) was a yellow oil, which after chromatography (petrol/ether - 80:20) gave benzylidene acetone (28 mg, 19%). The acidic fraction (214 mg) was a yellow foam which contained the title dione (n.m.r., see text), 5-phenyl resorcinol and benzene phenylthiosulphinate. From the n.m.r. integral there was 57% of the intermediate, 11% of the resorcinol and 6% of benzene phenylthiosulphinate. The yield quoted in Table I (i.e. 68%) corresponds to the sum of the calculated yields of the resorcinol and the intermediate.

Preparation of the α,β-unsaturated ketones (57)

Anisal acetone (57, R = p-C_6H_4-OMe) and furfurylidene acetone (57, R = 2-furyl) were prepared by the methods

described in Org. Syn., Coll. Vol. I, p.78 and p.283 respectively. 4-(p-nitrophenyl)-but-3-en-2-one (57, R = p-C_6H_4-NO_2) was obtained, in low yield, by a modification of a published procedure.[125] A solution of p-nitro benzaldehyde (15 g, 0.1 M) in acetone (16 g, 0.8 M) and water (10 ml) was chilled to 0^o and 10% aqueous sodium hydroxide (2.5 ml) added slowly. After 1 h the brown mixture was neutralised and extracted with ether. The washed organic phase gave a viscous red oil which was dissolved in concentrated sulphuric acid. After 5 min the mixture was poured onto ice when yellow crystals separated. Crystallisation from ethanol gave the title enone (2.11 g, 11%), as yellow crystals, m.p. 106-108^o (lit.[125] m.p. 110^o), δ2.46 (3 H, s), 6.92 (1 H, d, J = 16 Hz), 7.66 (1 H, d, J = 16 Hz), 7.80 (2 H, d, J = 9 Hz), 8.38 (2 H, d, J = 9 Hz).

Non-3-en-2-one (57, R = n-C_5H_{11})

A mixture of caproaldehyde (0.50 g, 5 mM) and dimethyl acetylmethylphosphonate (0.83 g, 5 mM) in dichloromethane (10 ml) was added slowly, dropwise to the stirred solution of sodium hydroxide (0.20 g, 5 mM) in water (10 ml) containing tetra-n-butylammonium bromide (25 mg). The two-phase system was vigorously agitated overnight. The layers were separated and the aqueous phase extracted with dichloromethane (2 x 10 ml). The washed and dried organic layer was evaporated to give the essentially pure title ketone (0.57 g, 82%), as a faintly yellow oil. A 500 mg portion was chromatographed (petrol/ethyl acetate - 95:5) to give the pure

compound (430 mg, 71%), as a colourless oil, ν_{max} 1670, 1625 cm^{-1}, δ0.90 (3 H, m), 1.20-1.60 (6 H, m), 2.16-2.40 (2 H, m), 2.24 (3 H, s), 6.04 (1 H, bd, J = 16 Hz), 6.80 (1 H, dt, J = 16, 6 Hz).

5-methyl-hex-3-en-2-one (57, R = iso-C_3H_7)

The procedure described above was followed, starting with iso-butyraldehyde (0.36, 5 mM). The crude product was, essentially, the title ketone (414 mg, 74%), a faintly yellow oil, ν_{max} 1675, 1625 cm^{-1}, δ1.08 (6 H, d, J = 7.5 Hz), 2.14 (3 H, s), 2.48 (1 H, m), 5.90 (1 H, bd, J = 16 Hz), 6.60 (1 H, dd, J = 16, 6 Hz). This material was used without further purification.

Adamantane-1-carbaldehyde

An attempt to convert adamantane-1-carboxylic acid to the aldehyde using the carbonyl di-imidazole procedure[126] failed. The acid was converted, with thionyl chloride, to the acid chloride (95%) m.p. 43-48° (lit.[61] m.p. 48.5-50°), ν_{max} 1795 and reduced with lithium tri-t-butoxyaluminium hydride[127] to give approximately 10% yield of the aldehyde (n.m.r.). A better method was a modified Rosenmund reduction.[128] The acid chloride (1.99 g, 10 mM) in dry THF (20 ml) was added slowly to the stirred suspension of hydrogen-equilibrated catalyst (10% Pd-C, 150 mg) in THF (30 ml) containing 2,6-lutidine (1.07 g, 10 mM). After the calculated volume (224 ml) of hydrogen was taken-up (ca. 5 h) the solvent was evaporated, the residue redissolved in petrol

and ether and filtered. The organic phase was washed with dil. HCl, water and brine. Evaporation of the solvent gave the crude aldehyde (1.84 g), ν_{max} 2700, 1730 cm^{-1}, δ1.6-2.2 (15 H, m), 9.15 (1 H, s). The aldehyde decomposed on standing overnight in a dichloromethane/deuteriochloroform solution.

5-(p-methoxyphenyl) resorcinol (55, R = p-C_6H_4-OMe)

Method A was used starting with MPSA (199 mg, 1 mM) and anisal acetone (176 mg, 1 mM). The reaction was carried out for 3 days at room temperature in the presence of eight-fold excess of magnesium methoxide. The usual work-up afforded: neutral fraction (109 mg), a yellow oil, which contained mainly the unreacted starting materials; acidic fraction - (220 mg), a yellow foam which was dissolved in benzene (50 ml) containing powdered calcium carbonate (∿20 mg) and pyrolysed (reflux, 5 h). The cooled solution was washed with dil HCl and water and evaporated to give a yellow-brown oil (185 mg). Addition of chloroform caused precipitation of a buff powder which was filtered to give the title resorcinol (129 mg, 60%), m.p. 152-153° (lit.[129] 158-159°), δ(d_6-acetone) 3.82 (3 H, s), 6.30 (1 H, t, J = 2 Hz), 6.56 (2 H, d, J = 2 Hz), 6.92 (2 H, d, J = 10 Hz), 7.43 (2 H, d, J = 10 Hz), 8.20 (2H, bs, exch.).

5-(2-furyl) resorcinol (55, R = 2-furyl)

Method A - 2 mM scale, five-fold excess of magnesium methoxide, room temperature, 2 days. The acidic fraction (450 mg) contained approximately 44% of the cyclohexanedione

intermediate (62), δ2.56-2.90 (1 H, m), 3.10-3.44 (1 H, m), 3.84 (1 H, bs), 3.96 (1 H, m), 5.70 (∿½ H, s), 5.80 (∿½ H, s), 5.94 (∿½ H, d, J = 2 Hz), 6.54 (∿½ H, d, J = 2 Hz), other signals were obscured by the peaks due to the resorcinol and benzene phenylthiosulphinate. The mixture contained approximately 19% of the former and 10% of the latter (n.m.r. integral). When the n.m.r. sample was heated the signals quoted disappeared. Pyrolysis of the remaining orange foam in benzene containing trimethyl phosphite (reflux, 6 h) gave a complex mixture whose n.m.r. spectrum showed a series of doublets (J = 12 Hz) in the region δ3.8-4.0.

Method B - MPSA (199 mg, 1 mM) in THF (4 ml) was added to the stirred suspension of sodium hydride (60%, 40 mg, ∿1 mM) in THF (5 ml). A colourless solution was obtained. After ½ h at room temperature the flask was immersed in an ice-bath and furfurylidene acetone (136 mg, 1 mM) in THF (2 ml) was added dropwise. The dark-brown solution was stirred overnight at room temperature. The reaction mixture was poured into ether and neutralised with dil HCl. The usual treatment of the organic phase afforded a brown oil (288 mg), which was triturated with petrol and chloroform. The dirty-white powder thus obtained was recrystallised from chloroform to give 5-(2-furyl) resorcinol (52 mg, 30%), as buff needles, m.p. 143-144°, ν_{max} 3200, 1618, 1440, 990, 840, 726 cm^{-1}, δ(d_6-acetone) 6.36 (1 H, t, J = 2 Hz), 6.50 (1 H, m, J = 1 Hz), 6.75 (1 H, d, J = 1 Hz), 6.76 (2 H, d, J = 2 Hz), 7.56 (1 H, d, J = 1 Hz), 8.4 (2 H, bs, exch.), (Found:

C, 67.99; H, 4.55. $C_{10}H_8O_3$ requires C, 68.18; H, 4.58). This compound darkens on exposure to light and air.

5-(p-nitrophenyl) resorcinol (55, R = p-C_6H_4-NO_2)

Method A - (1 mM scale), 8 equivalents of magnesium methoxide. The addition of the enone (191 mg, 1 mM) was performed at 0° and the reaction worked-up after stirring overnight. The neutral fraction gave a yellow gum (264 mg) which was chromatographed (chloroform/ethyl acetate - 85:15) to give a yellow solid (85 mg). Crystallisation from aqueous ethanol gave the title resorcinol (60 mg, 26%), as yellow crystals, m.p. 245-249° (dec) ν_{max} 3390, 1595, 1490, 1330, 1155, 830, 750 cm^{-1}, $\delta(d_6$-acetone) 6.47 (1 H, t, J = 2 Hz), 6.70 (2 H, d, J = 2 Hz), 7.81 (2 H, d, J = 10 Hz), 8.27 (2 H, d, J = 10 Hz), 8.63 (2 H, bs, exch.), (Found: C, 62.64; H, 3.93, N, 5.98. $C_{12}H_9NO_4$ requires C, 62.35; H, 3.92; N, 6.06).

Method B - (1 mM scale), as described for 5-(2-furyl) resorcinol except the addition of the enone was carried out at -60°. The dark-brown mixture was stirred overnight. An orange gum was obtained which was triturated with petrol and the residue recrystallised from aqueous ethanol to give the resorcinol (85 mg, 37%).

Olivetol (55, R = n-C_5H_{11})

Method A was used starting with non-3-en-2-one (140 mg, 1 mM), except that 6 equivalents of magnesium methoxide were employed. The reaction mixture was stirred overnight at

room temperature followed by 6 h at 50°. The usual work-up gave, from the acidic fraction, a yellow foam (182 mg) which consisted mainly of the cyclohexanedione intermediates (66) and (67) (58%) and olivetol (2%). The crude product was pyrolysed in refluxing benzene in the presence of powdered calcium carbonate during 4 h. Chromatography (chloroform/ ethyl acetate - 75:25) gave the title resorcinol (82 mg, 45%), as a pink oil which solidified on standing, m.p. 44-45° (lit.[15] m.p. 149°), δ(d_6-acetone) 0.82-0.96 (3 H, bt), 1.20-1.44 (6 H, m), 1.44-1.72 (2 H, m), 2.44 (2 H, bt, J = 7 Hz), 6.18 (3 H, s), 8.0 (2 H, bs, exch.).

Isolation of the intermediates (66) and (67)

The above experiment was repeated on a (10 mM) scale (total volume of methanol was approximately 150 ml); the reaction mixture was stirred for 4 days at room temperature. The usual work-up gave, from the acidic fraction, a yellow foam (2.05 g). Trituration of the crude product gave a white powder (361 mg) and a yellow oil. The white powder was washed with cold ether to give the pure syn-diastereoisomers (67) m.p. 124-130° (dec.), ν_{max} 3380, 1600, 1620, 1040, 750, 690 cm^{-1}, δ1.0 (3 H, m), 1.3-1.6 (6 H, m), 2.0 (2 H, m), 2.3-3.2 (3 H, m), 3.4 (1 H, m), 5.7 (1 H, s), 7.55 (5 H, bs), 7.4-7.6 (1 H, b, exch.), (Found: C, 66.46; H, 7.24. $C_{17}H_{22}O_3S$ requires C, 66.64; H, 7.24). The yellow oil was seen to contain the anti-isomers (66), together with a small amount of the syn-isomers, olivetol and the disproportionation products of phenylsulphenic acid. The oil was further

purified by the double extraction procedure. The new acidic fraction (1.086 g) was virtually free from the resorcinol (<5%). It contained mainly the anti-diastereoisomers (66), a yellow oil, δ0.9 (3 H, m), 1.0-1.5 (8 H, m), 2.3 (1 H, bd, J = 17 Hz), 2.6 (1 H, m), 3.15 (1 H, dd, J = 17, 7 Hz), 3.3 (1 H, bs), 5.62 (1 H, s), 7.5-7.7 (5 H, m), 9.5 (1 H, bs, exch.). After standing for 1 week at room temperature about 40% of the anti-isomers decomposed. This was easily seen since the olefinic proton of the anti-isomers was distinct from the corresponding proton in the syn-series. The oil was again subjected to the double extraction purification. A small portion (ca. 5 mg) in DMF (ca. 1 ml) was reduced with phosphorus tribromide (1 drop). The reaction (0°, 15 min) gave a mixture of polar and non-polar products. The polar material (t.l.c. in chloroform containing a few drops of acetic acid) consisted of two spots of similar R_f of which the less polar one was more intense.

Methylation of the cyclohexanedione intermediates (66) and (67)

The oil described above (302 mg) was subjected to chromatography (chloroform/ethyl acetate/acetic acid - 75:25:1.5) but despite several elutions the separation of the syn- and anti-isomers could not be achieved. The purified mixture (126 mg, syn-/anti-ratio ∿1:4) was dissolved in ether (10 ml) and an ethereal solution of diazomethane added dropwise until the yellow colour persisted. Evaporation of the solvent gave a pale-yellow oil (127 mg, 97%) which was a mixture of the four diastereoisomeric enol ethers designated Anti-A, Anti-B, Syn-A

and Syn-B. The Syn-A isomer precipitated on trituration with petrol and ether. Crystallisation from the latter solvent gave white, waxy crystals m.p. 129°, ν_{max} 1645, 1615, 1040 cm^{-1}. Repeated chromatography of the mother liquors gave: Syn-B, as a white powder (from ether), m.p. 95-115° (dec.), ν_{max} 1660, 1610, 1045 cm^{-1}, Anti-A, a pale-yellow oil, ν_{max} 1650, 1610, 1050 cm^{-1} and Anti-B, a similar oil, ν_{max} 1645, 1605, 1045 cm^{-1}. (For n.m.r. data see Table II.) (Found, for Syn-A: C, 67.35; H, 7.50. $C_{18}H_{24}O_3S$ requires C, 67.47; H, 7.54). The solid cyclohexanedione intermediates (67) (308 mg) were also methylated with diazomethane in anhydrous methanol. Evaporation of the solvent gave an oil (321 mg, 100%) which was, approximately, 1:1 mixture of Syn-A and Anti-B (n.m.r.). Traces of Syn-B were detected by t.l.c. Reduction of a small portion (ca. 5 mg) with phosphorus tribromide gave two less polar products of similar R_f. Trituration with ether and crystallisation from the same solvent gave Syn-A. The mother liquors after a fortnight at room temperature were found (n.m.r.) to contain olivetol mono-methyl ether in addition to Anti-B in approximately 1:2 ratio. The rates of decomposition of Anti-A and Anti-B, at room temperature, were roughly of the same order.

5-iso-propyl resorcinol (55, R = iso-C_3H_7)

Method A was followed starting with 5-methyl-hex-3-en-2-one (112 mg, 1 mM) and eight-fold excess of magnesium methoxide. The pale-yellow solution was stirred overnight at ambient temperature followed by 8 h at 50°. The usual work-up gave,

from the acidic fraction, a yellow foam (146 mg) which contained the intermediate (81) (38%), δ0.72 (6 H, d, J = 7 Hz), 1.64 (1 H, m), 2.30 (1 H, m), 2.39 (1 H, bd, J = 18 Hz) and 3.05 (1 H, dd, J = 18, 7 Hz) forming an ABq, 3.40 (1 H, bs), 5.64 (1 H, s), 7.4-7.6 (5 H, m), 8.8 (1 H, exch.), the resorcinol (3%) and phenylsulphinylacetic acid (15%). The neutral fraction (93 mg), a yellow oil, consisted mainly of unreacted MPSA and self-condensation products of the enone. The yellow foam was thermolysed in benzene (3 h) and the crude oil chromatographed (chloroform/ethyl acetate - 85:15) to give the title resorcinol (45 mg, 30%), as a faintly pink oil, ν_{max} 3300, 1600, 1140, 985, 835 cm^{-1}, δ1.14 (6 H, d, J = 7Hz), 2.72 (1 H, m, J = 7 Hz), 6.15 (1 H, bs), 6.24 (2 H, bs), 6 (2 H, exch.), (Found: M^+ 152.0833. $C_9H_{12}O_2$ requires 152.0837). A minor, less polar product was identified as 2-phenylthio-5-iso-propyl resorcinol (84) (11 mg, 4%), an oil, ν_{max} 3370, 1590, 845, 740, 690 cm^{-1}, δ1.08 (6 H, d, J = 7 Hz), 3.44 (1 H, m, J = 7 Hz), 6.38 (2 H, s), 6.8-7.2 (5 H, m). Treatment with acetic anhydride and pyridine gave the diacetate, 1,3-di-acetoxy-2-phenylthio-5-iso-propyl benzene (85), as an oil, ν_{max} 1760, 1590, 1015, 895, 740, 690 cm^{-1}, δ1.12 (6 H, d, J = 7 Hz), 2.08 (3 H, s), 2.28 (3 H, s), 3.65 (1 H, m, J = 7 Hz), 6.8-7.2 (7 H, m), (Found: M^+ 344.1090. $C_{19}H_{20}O_4S$ requires 344.1083).

3-phenyl-5-methyl phenol (86)

Phenylsulphinylacetone (PSA) (182 mg, 1 mM) in dry methanol (5 ml) was added to a solution of magnesium meth-

oxide (150 mg, 6 mM) in methanol (5 ml). After 15 min benzylidene acetone (146 mg, 1 mM) in methanol (5 ml) was injected and the pale-yellow solution stirred overnight at room temperature before heating it to reflux for 24 h. The solvent was removed in vacuo and the residual, orange oil was partitioned between ether and dil. HCl. After further extraction of the aqueous phase the combined ethereal layer was washed with saturated aqueous sodium hydrogen carbonate then dried and evaporated to give a yellow oil (254 mg). A portion (160 mg) was chromatographed (chloroform/petrol - 60:40 rising to 80:20) to give the phenol (76 mg, 62%) as an oil. Trituration with petrol gave a white powder which was recrystallised from hexane to give white, fluffy crystals, m.p. 53-55° (lit.[130] m.p. 56°), ν_{max} 3350, 1600, 850, 760, 700 cm^{-1}, δ2.36 (3 H, s), 6.65 (1 H, bs), 6.88 (1 H, bs), 7.00 (1 H, bs), 7.30-7.65 (5 H, m), 5.00 (1 H, bs, exch.). (Found: C, 84.45; H, 6.68. $C_{13}H_{12}O$ requires C, 84.75; H, 6.56).

The same product was formed when the reaction was performed with sodium hydride in THF (although the yield was not determined). PSA (184 g, 1 mM) in THF (4 ml) was added to the stirred suspension of sodium hydride (60%, 40 mg, 1 mM) in THF (5 ml). After the evolution of hydrogen ceased, the clear solution was stirred at room temperature for ½ h and benzylidene acetone (146 mg, 1 mM) in THF (2 ml) added at 0°. After stirring the mixture at room temperature overnight the usual, aqueous work-up gave an oil which was triturated with ether to give a small amount (ca. 5 mg) of an

unstable, very polar, white solid. The solid turned brown on standing at room temperature. T.l.c. analysis showed that the material was decomposing to the phenol and unidentified products. The residual oil was triturated with petrol and crystallisation of the white powder thus obtained furnished the phenol (86).

2-Ethyl-3-methyl-5-phenyl phenol (90)

The magnesium methoxide method described above was used starting with 1-phenylsulphinyl-pentan-2-one (89) (214 mg, 1 mM) and a four-fold excess of the base. The reaction mixture was stirred overnight at room temperature followed by 4 h at reflux. The usual work-up gave a yellow oil (311 mg) which was chromatographed (chloroform) to give the title phenol (93 mg, 44%), as colourless oil which solidified at 0^{o} to give m.p. 35-40^{o}, ν_{max} 3250, 1580, 850, 760, 690 cm^{-1}, δ1.16 (3 H, t, J = 7.5 Hz), 2.35 (3 H, s), 2.72 (2 H, q, J = 7.5 Hz), 6.89 (1 H, bs), 7.06 (1 H, bs), 7.3-7.7 (5 H, m), 5.5 (1 H, bs, exch.). (Found: C, 84.62; H, 7.70. $C_{15}H_{16}O$ requires C, 84.86; H, 7.60).

Use of the sodium hydride/THF method gave a yellow oil (281 mg) which was chromatographed (petrol/ether - 75:25) to give the phenol (100 mg, 47%), benzylidene acetone (31 mg, 21%) and a more polar (R_f 0.15), unknown compound (43 mg).

Attempted preparation of methyl orsellinate (106)

Dimethyl ethylidene malonate (105) (158 mg, 1 mM) was added slowly in THF (4 ml) to a 0.2 M solution of the sodium

enolate of PSA (182 mg, 1 mM). The resultant yellow solution was allowed to warm to room temperature and stirring was continued for a further 6 h. Ether and water were added. The aqueous, alkaline layer was made acid and extracted with ethyl acetate. The acidic fraction (brown oil, 176 mg) was taken up in ether and washed with saturated sodium hydrogen carbonate in the usual manner. The new neutral fraction (94 mg) contained some methyl orsellinate (by n.m.r. analysis). The spectrum of the new acidic portion (66 mg) was very complex. Pyrolysis of the latter in refluxing benzene (5 h) simplified the spectrum and resulted in formation of the orsellinic ester. Chromatography (chloroform/ethyl acetate - 45:5) of the combined neutral fraction and the thermolysis mixture gave impure methyl orsellinate (55 mg) as an orange oil, δ2.46 (3 H, s), 3.92 (3 H, s), 6.26 (1 H, bs), 6.35 (1 H, bs), 8.0 (1 H, bs, exch.), 11.64 (1 H, s, exch.).

Reactions with ethyl benzylidene acetoacetate (110)

Ethyl benzylidene acetoacetate was prepared according to the procedure described in Org. Syn. Coll. Vol. IV, p.408. Benzaldehyde (11.6 g, 0.11 M), ethyl acetoacetate (13 g, 0.10 M), piperidine (0.4 ml), acetic acid (1.2 ml) and benzene (10 ml) were refluxed under a Dean-Stark separator until no more water collected (ca. 2 h). The resultant yellow solution was poured into ether (100 ml) and washed with 20 ml portions of dil. HCl (5%), aqueous sodium hydrogen carbonate (5%), acetic acid (5%) and water till

neutral. The organic phase was dried, evaporated and the residual oil distilled to give a faintly yellow oil (16.5 g, 62%) b.p. 116-120°/0.7 mm, which was a mixture of geometric isomers. The i.r. and n.m.r. data of the two isomers are given in the section describing the preparation of the chlorosulphide (145).

The sodium enolate of MPSA (198 mg, 1 mM) was prepared in the usual way (1 mM NaH, 6 ml THF). Ethyl benzylidene acetoacetate (218 mg, 1 mM) in THF (2 ml) was added and the resultant yellow solution was stirred overnight at 60°. The solvent was removed, in vacuo, and the residual orange oil partitioned between ether and dil. HCl. The organic phase yielded an orange oil (240 mg) which was chromatographed (chloroform) to give 2-methyl-3-carbethoxy-4-phenyl-5-carbomethoxy-4,5-dihydrofuran (112) (55 mg, 19%), as an oil, ν_{max} 1755, 1700, 1650, 1210, 1085, 1030, 760, 700 cm^{-1}, δ1.08 (3 H, t, J = 7 Hz), 2.40 (3 H, bs), 3.87 (3 H, s), 4.07 (2 H, q, J = 7 Hz), 4.48 (1 H, bd, J = 5 Hz), 4.90 (1 H, d, J = 5 Hz), 7.35 (5 H, bs), (Found: M^+ 290.1137. $C_{16}H_{18}O_5$ requires 290.1154).

On standing the dihydrofuran (112) was slowly saponified to the acid (114), ν_{max} 3400-2500, 1720, 1700, 1650, 1205, 1085, 1030, 760, 700, δ1.10 (3 H, t, J = 7 Hz), 2.43 (3 H, bs), 4.06 (2 H, q, J = 7 Hz), 4.55 (1 H, bd, J = 5 Hz), 4.92 (1 H, d, J = 5 Hz), 7.33 (5 H, bs) and one exchangeable proton. Treatment of the acid (114) with diazomethane returned the ester (112).

PSA (182 mg, 1 mM) was reacted in an analogous manner

with (110) (218 mg, 1 mM) to give an orange-brown oil (201 mg), whose n.m.r. spectrum showed δ1.02 (3 H, t, J = 7 Hz), 2.18 (3 H, s), 2.36 (3 H, bs), 3.96 (2 H, q, J = 7 Hz), 4.36 (1 H, bd, J = 5 Hz), 4.68 (1 H, d, J = 5 Hz), 7.2 (5 H, bs). The 2-methyl-3-carbethoxy-4-phenyl-5-acetyl-4,5-dihydrofuran structure (115) was therefore assigned to the major product.

A similar reaction (1 mM scale) of the sodium enolate of methyl(phenylsulphonyl)acetate gave an orange oil (240 mg) which contained a small amount of the dihydrofuran (112), by n.m.r. and t.l.c. analysis.

Reaction of phenylthioacetone with methyl crotonate

Phenylthioacetone (166 mg, 1 mM) in THF (3 ml) was added to the stirred suspension of sodium hydride (60%, 45 mg, 1 mM) in THF (5 ml) at 0^{o}. A yellow solution was obtained. After stirring for a further ½ h at room temperature methyl crotonate (103 mg, 1 mM) in THF (2 ml) was added rapidly. The reaction mixture was stirred overnight at room temperature. The brown solution was worked-up in the normal way to give a yellow oil (201 mg). Chromatography (chloroform/ethyl acetate/acetic acid - 80:20:0.3) gave two major products of similar R_f. The slightly more polar material was identified as 5-methyl-4-phenylthiocyclohexane-1,3-dione (118) (158 mg, 20%), an oil, ν_{max} 3300, 1590, 750, 690 cm^{-1}, δ1.04-1.36 (3 H, m), 2.2-4.2 (4 H, complex patterns), 5.52 (s) and 5.62 (s) total 1 H, 7.35-7.60 (5 H, m), 8.5 (1 H, bs, exch.). (Found: M^{+}

234.0717. $C_{13}H_{14}O_2S$ requires 234.0715). Addition of twenty-fold excess of TFA to the n.m.r. sample simplified the spectrum (Fig. 15). The less polar material was assigned the 3-methyl-4-phenylthio-5-oxo-hexanoic acid structure (121) (31 mg, 13%), an oil, ν_{max} 3300-2600, 1700 (1715 sh), 750, 690 cm^{-1}, δ1.08 (d, J = 7 Hz) and 1.30 (d, J = 7 Hz) total area 3 H, 2.30 (3 H, s), 2.3-2.7 (3 H, m), 3.55-3.85 (1 H, m), 7.3-7.6 (5 H, m), 11.8 (1 H, bs, exch.).

Phenylsulphinylacetic acid (127)

Phenylthioacetic acid (1.68 g, 10 mM) was oxidised with sodium metaperiodate (2.14 g, 10 mM) in aqueous methanol. After 8 h the reaction was worked-up as described previously (PSA) to give a faintly yellow solid (1.68 g, 91%). Crystallisation from ethyl acetate gave the title acid, m.p. 110-112° (lit.[131] m.p. 116), δ3.88 (2 H, ABq, J = 14 Hz), 7.5-7.8 (5 H, m), 10.2 (1 H, s, exch.).

1-phenylsulphinyl-pentan-2-one (89)

To a solution of di-isopropylamine (2.21 g, 21 mM) in THF (10 ml) n-butyl-lithium (1.4 M, 15 ml, 21 mM) was added. The cold (-5°) solution was stirred for 15 min and PSA (1.82 g, 10 mM) in THF (15 ml) was added slowly dropwise. The resultant orange-red solution was stirred for a further ½ h and ethyl bromide (1.20 g, 11 mM) in THF (5 ml) injected. After stirring overnight at room temperature a yellow solution and a white precipitate were obtained. Ether and dil. HCl were added and the organic phase was processed in

the usual way to give essentially pure product (1.72 g, 81%), as a yellow solid. Crystallisation from ether gave the analytically pure title ketone, m.p. 61-63°, ν_{max} 1700, 1030, 730, 690, δ0.88 (3 H, t, J = 7 Hz), 1.56 (2 H, m, J = 7 Hz), 2.46 (2 H, t, J = 7 Hz), 3.84 (2 H, ABq, J = 13 Hz), 7.45-7.74 (5 H, m). (Found: C, 62.92; H, 6.80. $C_{11}H_{14}O_2S$ requires C, 62.83; H, 6.71).

1-phenylsulphinyl-5-methyl-hex-5-en-2-one (129)

The dianion of PSA (1.82 g, 10 mM) was alkylated with methallyl chloride (0.91 g, 10 mM) as described above. The crude product (1.94 g, 82%) was a yellow oil. Chromatography (petrol/ether - 70:30 rising to 60:40) of a small portion gave the analytically pure title ketone, a waxy solid, m.p. 33-37°, ν_{max} 1705, 1640, 1030, 890, 730, 690 cm^{-1}, δ1.72 (3 H, bs), 2.28 (2 H, bt, J ∿ 7 Hz), 2.68 (2 H, bt, J ∿ 7 Hz), 3.93 (2 H, ABq, J = 14 Hz), 4.71 (1 H, bs), 4.80 (1 H, bs), 7.6-7.9 (5 H, m). (Found: C, 65.89; H, 6.65. $C_{13}H_{16}O_2S$ requires C, 66.08; H, 6.82).

Attempts to cyclise the hexenone (129)

Heating (129) in refluxing benzene overnight gave the starting material. A similar result was obtained in refluxing toluene (18 h). Heating the keto sulphoxide (129) (76 mg, 0.32 mM) in refluxing benzene (20 ml) containing a catalytic amount of p-toluenesulphonic acid gave a brown oil (60 mg) whose n.m.r. spectrum showed, amongst other signals, a three-proton singlet at δ2.24 and a four-proton ABq (J =

10 Hz) and δ6.68 and 6.62. The oil was taken up in ether and washed with dilute, aqueous sodium hydroxide. The aqueous layer was acidified (conc. HCl) and extracted with dichloromethane to give p-cresol (4 mg, 11%), identical (t.l.c.) with an authentic sample.

The keto sulphoxide (129) (89 mg, 0.38 mM) was dissolved in deuteriochloroform and a two-fold excess of TFA added. After 26 h at room temperature the reaction, as monitored by n.m.r., was complete. The brown mixture was poured into ether and shaken with saturated, aqueous sodium hydrogen carbonate. The ethereal layer was further washed with water, dried and evaporated to give an orange-brown oil (73 mg). The crude products were chromatographed (dichloromethane/ ethyl acetate - 95:5 and 90:10) to give a yellow oil (30 mg, 33%), which was a mixture of the three cyclic ethers (131), (132) and (133), ν_{max} 3300, 1705, 1630 (1610 sh), 1250, 1040 (v.s.), 750, 690 cm^{-1}, δ1.25-1.50 (6 H, m) δ2.0 (3¼ H, m), 2.9 (3/4 H, m), 3.2 (1 H, m), 5.2 (1/8 H, bs), 5.6 (3/8 H, bs), 7.5-7.8 (5 H, m), 5.4 (½ H, exch.). The calculated amounts of the three ethers were (131) - 37.5%, (132) - 12.5%, (133) - 50%.

m-Methoxy benzyl chloride

m-Methoxy benzaldehyde (1.5 g, 11 mM) was reduced with sodium borohydride (400 mg) in ethanol (20 ml). After 2 h the mixture was neutralised (conc. HCl) and the solvent removed in vacuo. The residue was taken up in ether, filtered, and the solvent evaporated to give m-methoxy

benzyl alcohol (1.36 g, 90%), a colourless oil, δ3.84 (3 H, s), 4.65 (2 H, s), 6.9 (3 H, m), 7.3 (1 H, t, J = 8 Hz).

m-Methoxy benzyl alcohol (2.4 g, 17.4 mM) was dissolved in pyridine (1.6 ml, ∿15 mM) and thionyl chloride (1.4 ml, 20 mM) added at 0^{o}. The stirred reaction mixture was allowed to warm to room temperature during 4 h. Toluene was added, the precipitate filtered, the solvent removed in vacuo and the residual oil distilled at 10 mm Hg collecting the title compound boiling in the range 115-120^{o}, (2.21 g, 81%), (lit.[132] b.p. 112-115^{o}/10 mm), δ3.84 (3 H, s), 4.60 (2 H, s), 6.96 (3 H, m), 7.52 (1 H, bt, J = 8 Hz).

4-(m-methoxyphenyl)-1-(phenylsulphinyl)-butan-2-one (134)

The dianion of PSA (183 mg, 1 mM) was alkylated with m-methoxy benzyl chloride (182 mg, 1.02 mM) as described previously. After 16 h the usual work-up afforded a yellow oil (282 mg). A portion (200 mg) was chromatographed (petrol/ethyl acetate - 70:30) to give the title keto sulphoxide (91 mg, 41%), a pale-yellow solid which was recrystallised from ether to give white crystals, m.p. 54-55^{o}, ν_{max} 1700, 1610, 1085, 1040, 885, 780, 740, 690 cm^{-1}, δ2.82 (4 H, bs), 3.78 (3 H, s), 3.82 (2 H, ABq, J = 14 Hz), 6.76 (3 H, bd, J ∿ 6 Hz), 7.20 (1 H, bt, J ∿ 6 Hz), 7.4-7.7 (5 H, m). (Found: C, 67.80; H, 5.75. $C_{17}H_{18}O_3S$ requires C, 67.53; H, 6.00).

A non-polar band (30 mg, 15%) was 1,2-di(m-methoxyphenyl)-ethyl chloride (135), δ3.34 (2 H, d, J = 7 Hz), 3.78 (3 H, s), 3.82 (3 H, s), 5.06 (1 H, t, J = 7 Hz), 6.7-7.4 (8 H, m).

The crude sulphoxide (134) (80 mg) was pyrolysed in refluxing toluene (16 h). A complex mixture of non-polar products was obtained (t.l.c.). The appearance of a singlet at δ4.64 in the n.m.r. spectrum of the crude products indicated that the keto sulphide (136) had formed. The pure keto sulphoxide (134) was virtually inert under identical conditions.

Methyl dibromoisobutyrate (140)

Diethyl bis(hydroxymethyl)malonate was prepared as described in Org. Syn. Coll. Vol. V, p.381.

The low-melting crystals of diethyl bis(hydroxymethyl)-malonate (55 g, 0.25 M) were heated with 48% hydrobromic acid (420 ml, 4 mM), for 3 h during which time approximately 20 ml of ethyl bromide was collected together with the aqueous distillate. The mixture was refluxed for a further 5 h and the brown solution cooled overnight. The crystals were filtered and the mother liquors concentrated and chilled to afford the second crop. The combined yield of the crude dibromo-isobutyric acid was 24.3 g (40%). Recrystallisation from water gave 12.5 g of material m.p. 93-100° (lit.[133] m.p. 100-103°).

The purified acid (10 g, 40 mM) was dissolved in methanol (15 ml) and thionyl chloride (4 ml, 50 mM) added dropwise at 0°. After stirring overnight the solvent was removed in vacuo and the residual oil taken up in ether. The organic phase was washed with dilute aqueous sodium hydrogen carbonate, water, dried and evaporated to give the title ester,

(8.8 g, 85%), a nearly colourless oil, δ3.24 (1 H, m, J = 6 Hz), 3.78 (4 H, d, J = 6 Hz), 3.84 (3 H, s). The crude ester was used directly in the next step.

Methyl α-bromomethylacrylate (139)

The crude methyl ester (140) (2.60 g, 10 mM) was dissolved in ether (20 ml) and triethylamine (1.4 ml, 10 mM) added to the stirred solution at 0^{o}. An exothermic reaction took place and a heavy white precipitate appeared. After stirring the mixture for a further 1 h at room temperature it was diluted with ether and acidified with dil. HCl. The organic layer was washed with water, dried and evaporated to give the starting material (1.30 g, 50%). The aqueous layer was evaporated to dryness. The solid residue was a mixture of triethylamine hydrobromide and (methyl methacrylyl)triethylammonium bromide (141), δ1.48 (9 H, t, J = 7 Hz), 3.50 (6 H, q, J = 7 Hz), 3.88 (3 H, s), 4.56 (2 H, bs), 6.84 (1 H, s), 6.92 (1 H, s).

A solution of lithium di-isopropylamide (from 1.01 g of the amine and 6.7 ml of 1.5 M n-butyl-lithium) in THF (ca. 20 ml) was chilled to -78^{o} and the crude ester (140) (2.60 g, 10 mM) added rapidly in small (ca. 5 ml) volume of THF. The resultant brown solution was worked-up in the usual way after ½ h. The ethereal phase gave a pale-brown oil (1.01 g, 56%) which was mainly the ester (139). Distillation gave the pure title compound (0.85 g, 48%), as a colourless oil, b.p. $90\text{-}92^{o}$/36 mm ν_{max} 1715, 1640, 960 cm^{-1}, δ3.86 (3 H, s), 4.22 (2 H, bs), 6.04 (1 H, bs), 6.42 (1 H, s).

Attempted alkylation of the dianion of PSA with methyl α-bromomethyl acrylate (139)

The dianion of PSA (182 mg, 1 mM) in THF was generated as described previously. After stirring the orange solution for 1 h at -5° the flask was chilled to -70° and bromo ester (139) (179 mg, 1 mM) in THF (5 ml) added dropwise. There was an immediate colour discharge and a pale-yellow solution was obtained. The reaction mixture was stirred for a further 1½ h aquiring room temperature and quenched with saturated aqueous ammonium chloride. The aqueous phase was extracted with ether and the combined organic layer processed in the usual way to yield a yellow oil and a solid (210 mg). Chromatography (chloroform/ethyl acetate - 80:20) gave a faintly yellow oil (42 mg) which was a 1:1 mixture of PSA (9%) and 1-phenylsulphinyl-5-carbomethoxy-hex-5-en-2-one (143) (9%), δ2.5-2.8 (4 H, m), 3.84 (3 H, s), 3.92 (2 H, ABq, J ∿ 14 Hz), 5.64 (1 H, bs), 6.22 (1 H, s), 7.6-7.8 (5 H, m).

1-Phenylthio-1-chloro-2-propanone (145)

The sodium enolate of PSA (182 mg, 1 mM) in THF was generated in the normal manner and trimethylsilyl chloride (0.5 ml, 4 mM) added. A "soapy" white precipitate was observed. Ethyl benzylidene acetoacetate (110) (218 mg, 1 mM) in THF (3 ml) was then added and the mixture refluxed overnight. The usual aqueous work-up gave, from the ethereal solution a yellow oil (385 mg) which was chromatographed (petrol/ethyl acetate - 95:5 then 90:10) to give the two isomers of ethyl benzylidene acetoacetate, viz., Z - (63 mg,

29%), oil, ν_{max} 1725, 1660, 1620, 755, 690, δ1.24 (3 H, t, J = 7.5 Hz), 2.40 (3 H, s), 4.32 (2 H, q, J = 7.5 Hz), 7.4 (5 H, m), 7.54 (1 H, s), E - (58 mg, 27%), oil, ν_{max} 1715, 1690, 1620, 770, 690, δ1.32 (3 H, t, J = 7 Hz), 2.34 (3 H, s), 4.28 (2 H, q, J = 7 Hz), 7.38 (5 H, bs), 7.64 (1 H, s), and the title ketone (130 mg, 64%), a yellow oil, ν_{max} 1720, 690, δ2.30 (3 H, s), 5.50 (1 H, s), 7.25-7.55 (5 H, m).

In a similar experiment MPSA was converted to methyl (phenylthio)chloroacetate (146), δ3.80 (3 H, s), 5.52 (1 H, s), 7.3-7.6 (5 H, m).

Methyl (2E)-5-phenyl-2-(phenylsulphinyl)pent-2-enoate (157)

The sodium enolate of MPSA was prepared by the dropwise addition of the ester (198 mg, 1 mM, 3 ml THF) to the stirred suspension of sodium hydride (60%, 42 mg, 1 mM, 3 ml THF) at 0^{o}. After the evolution of hydrogen ceased the clear solution was stirred for a further ½ h at room temperature. The flask was immersed in an ice-bath and a solution of anhydrous zinc chloride (144 mg, 1.06 mM) in THF (2 ml) added. A transient, milky precipitate was observed. After stirring for another ½ h at 0^{o} 3-phenylpropionaldehyde (140 mg, 1.04 mM) in THF (2 ml) was added rapidly. The solution was stirred overnight and then refluxed for 3 h when a bright-white precipitate was obtained. The reaction was worked-up by adding saturated aqueous ammonium chloride and ether. The organic phase was processed in the usual way to yield a yellow oil (270 mg). A portion (200 mg) was chromatographed (petrol/ethyl acetate - 85:15) to give the unreacted

MPSA (22 mg, 15%) and the title ester (117 mg, 50%), a pale-yellow oil, ν_{max} 1710, 1625, 1210, 1040, 750, 690 cm^{-1}, δ2.8-3.3 (4 H, m), 3.70 (3 H, s), 7.2-7.4 (6 H, bs), 7.4-7.7 (5 H, m). (Found: C, 68.52; H, 5.62. $C_{18}H_{18}O_3S$ requires C, 68.77; H, 5.77.) On storage below 0^o the oil deposited colourless crystals m.p. 33-36^o. Based on recovered MPSA the yield was 59%.

Methyl (2E)-4-hydroxy-5-phenylpent-2-enoate (164)

The ester sulphoxide (157) (78 mg, 0.25 mM) was dissolved in ether (6 ml) and triethylamine (0.12 ml, 0.84 mM) followed by trimethyl phosphite (4 drops, 1 mM) added. The solution was refluxed overnight, diluted with ether and washed with saturated, aqueous sodium hydrogen carbonate, dil. HCl, water and brine. Evaporation of the dried, organic extract gave a yellow oil (82 mg) which was chromatographed (dichloromethane/ethyl acetate - 98:2 followed by 95:5) to give the hydroxy ester (164) (19 mg, 36%), as an oil, ν_{max} 3400, 1720, 1655, 1260, 700, 650 cm^{-1}, (n.m.r. see Table IV). (Found: C, 70.04; H, 6.83. $C_{12}H_{14}O_3$ requires C, 69.88; H, 6.84.) A slightly more polar compound was the dimethyl phosphate ester (165) (25 mg, 32%), an oil, ν_{max} 1720, 1660, 1270 (vs), 1040 (vs), 750, 700 cm^{-1}, δ (see Table IV). The phosphate ester (165) was slowly hydrolysed by aqueous potassium hydroxide (2 weeks at room temperature) to give the hydroxy acid (166), δ (see Table IV). Methylation (diazomethane) gave material identical to the hydroxy ester (164) (t.l.c.).

Methyl 3,4-dimethyl-6-(2'-phenyl)ethylcyclohexa-1,3-diene-1-carboxylate (172)

In a qualitative experiment, the conjugated ester sulphoxide (2 drops) was dissolved in 2,3-dimethylbuta-1,3-diene (10 drops) and the solution refluxed overnight. The brown oil was chromatographed (petrol/ethyl acetate - 97:3) to give (in order of elution), diphenyl disulphide, methyl 4,5-dimethyl-2-(2'-phenyl)ethylbenzoate (173), δ (see text) and the dienoic ester (172).

The reaction was repeated with the ester sulphoxide (173 mg, 0.55 mM) in the diene (2 ml) in a sealed tube which was heated at 80° for 2 days. The unreacted diene was removed *in vacuo* and the residual oil (200 mg) chromatographed (petrol/ether - 90:10) to give the *title ester* (89 mg, 60%), as a colourless oil, λ_{max} 313 nm (ε 4500), ν_{max} 1700, 1650, 1585, 1280, 1230, 750, 700 cm^{-1}, δ1.52-1.88 (2 H, m), 1.80 (6 H, bs), 2.05-2.90 (5 H, m), 3.76 (3 H, s), 6.96 (1 H, bs), 7.1-7.3 (5 H, m). (Found: C, 80.09; H, 8.34. $C_{18}H_{22}O_2$ requires C, 79.96; H, 8.20).

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