TRENT POLYTECHNIC
in collaboration with
I.C.I. LTD., PHARMACEUTICALS DIVISION

Synthesis and Reactions of Heterocyclic Sulphur Compounds

being a thesis submitted to
the Council for National Academic Awards
for the degree of
Doctor of Philosophy
by

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March, 1981

To Pauline, Paul and Anna

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PREFACE

The work described in this thesis was carried out by the author in the laboratories of the Department of Physical Sciences, Trent Polytechnic, Nottingham, between September 1977 and September 1980. A period of three months was spent at the collaborating establishment, I.C.I. Pharmaceuticals Division, Alderley Edge, in fulfilment of the requirements of the CASE* award scheme, funded by the Science Research Council.

Tribute must be paid to the late Dr. U. Eisner, for her untiring and dedicated supervision despite frequent ill health. The author wishes to thank Dr. J.P. Cairns of I.C.I. Pharmaceuticals Division, whose guidance has been invaluable throughout the course of the work. Special thanks are due also to Dr. J.M. Barker for help and advice, particularly in the final stages of the work.

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Alan Spreadbury

ALAN CHARLES SPREADBURY
TRENT POLYTECHNIC

*Co-operative award in science and engineering.

DECLARATIONS

Alan C. SPREADBURY

a) The candidate declares that while working for this award he was not registered for any other CNAA or University award and that none of the work included in this thesis has been submitted for any other degree or award.

b) During the period of research the candidate has attended the following specialist lecture courses in the Polytechnic:-

   i) Advanced nmr spectroscopy.

   ii) Biosynthesis.

   iii) Substituent effects in organic chemistry..

SYNTHESIS AND REACTIONS OF HETEROCYCLIC SULPHUR COMPOUNDS

A.C. SPREADBURY

ABSTRACT

This thesis describes the synthesis of substituted m-dithiins by the reaction of acetylenic esters with aromatic aldehydes and hydrogen sulphide in the presence of boron trifluoride etherate, and their thermal rearrangement to the corresponding 3,4-dihydro-o-dithiins. Chemical evidence is presented for the proposed mechanism of formation of the 3,4-dihydro-o-dithiins, and the stereochemistry and reactions of the m- and o-dithiins are discussed.

The preparation of several new m-dithiin analogues and their thermal rearrangement was carried out. Treatment of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate with n-butyllithium followed by water resulted in a prototropic shift and the formation of a tautomeric m-dithiin. Reaction of the deprotonated species with appropriate electrophiles afforded deutero-, methyl- and acetyl-substituted m-dithiins. The two tautomeric m-dithiins were the subject of X-ray crystallographic determinations, which furnished information regarding their configuration and conformation.

Oxidation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate gave a mixture of monosulphoxide isomers which were separated and their configuration assigned. The same m-dithiin, when treated with aqueous base, suffered an unusual sulphur extrusion yielding a thiophen; the mechanism of this transformation is considered.

Cis and trans isomers of dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate were isolated, and their configurations were assigned by spectroscopic and chemical means. Attempts were made to form anhydro-o-dithiins, first by direct dehydrogenation, then by other routes involving oxidation followed by halogenation.

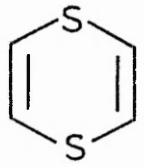
Desulphurisation of 3,4-dihydro-o-dithiins with trivalent phosphorus reagents gave stereospecific conversion to a series of new and previously inaccessible 2,3-dihydrothiophens; these were converted by dehydrogenation into thiophens.

Initial attempts to hydrolyse vicinal dicarboxylic ester groups in both m- and o-dithiins were unsuccessful, as were attempts to form the required diacids by the protection, cyclisation and deprotection of acetylenedicarboxylic acid. Reaction of the diesters, however, with boron trifluoride etherate in the presence of water, led to the isolation in high yield of the corresponding carboxylic anhydrides. The required diacids were prepared from these by standard methods.

GENERAL INTRODUCTION

m- and o-Dithiins; Structure and Reactivity

The chemistry of o- and m-dithiins (2,3) has been rather neglected in comparison with that of the p-dithiin ring system[1,2] (1). Not surprisingly this is a reflection of the instability of these compounds; o-dithiin (2) was first isolated as red crystals by Schroth[3] and co-workers in 1965 who found that it readily polymerised and extruded sulphur, forming thiophen. m-Dithiin (3) has never been isolated, although recently[4] its intermediacy in the photoreduction of aromatic ketones with thioethers has been indicated by esr/CIDNP* techniques.



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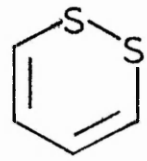

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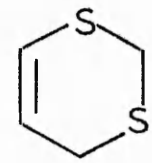


(3)

o-Dithiins such as 2 are cyclic dienes containing a disulphide bond, and as such, they possess 8 π -electrons within the ring. Hückel's rule states that only planar, conjugated cyclic molecules containing $(4n + 2)$ π electrons (n=0,1,2 etc.) can be considered as aromatic. Molecules

* CIDNP (chemically induced dynamic nuclear polarisation) involves the observation of nmr signals from the products of a free radical reaction as the reaction proceeds.

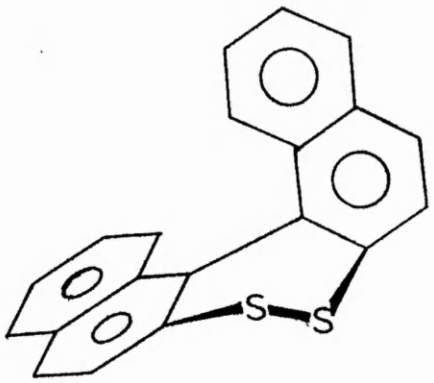
such as o-dithiin (2) which contain 4n π-electrons (n=2) can therefore be termed nonaromatic or anti-aromatic, and might be expected to behave like nonaromatic conjugated dienes. The dihedral angle between the two C-S bonds in the state of minimum repulsion of nonbonded p electrons, would be about 90°; that for o-dithiin (2) is probably around 50°. Thus, to avoid strain, the molecule adopts a non-planar conformation in which p orbital overlap is greatly diminished.

Salmond[5] has observed in o-dithiin (2) the lack of any properties consistent with cyclic delocalisation.

Fused o-dithiins such as dinaphtho [c,e] -o-dithiin (4) have been isolated[6] as enantiomeric conformers, and their absolute configurations have been deduced[7].

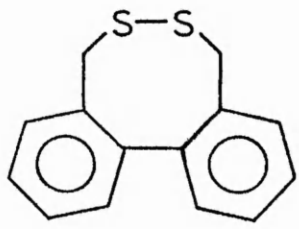
(4)

+ or −



Undoubtedly, a factor having some bearing on the existence of stable enantiomeric conformers of 4 is the restricted rotation imposed by the close proximity of the naphthyl groups, but the contribution of the disulphide bond to the height of the rotational barrier must also constitute an important factor. A further example of the resolution of enantiomeric conformers of a cyclic disulphide has been

reported by Lüttringhaus[8], who resolved the disulphide 5 into its optical isomers and calculated the energy barrier to rotation as 28.8 kcal mol^{-1}.

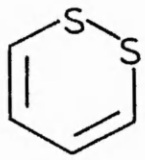


(5)

The strain imposed on the o-dithiin system by the presence of the disulphide bond is therefore likely to be an important factor in its reactions.

Although p-dithiin (1) contains 8 π -electrons, it is a stable compound. It does not exhibit aromatic properties, but nevertheless is not affected in many procedures which cause reaction in vinyl sulphides[5]. This extra stabilisation has been attributed[9] to the involvement of d orbitals of the sulphur atoms, especially as the ring is known to exist in a boat conformation[1] and p orbital delocalisation is minimal. If this argument were valid, a degree of d orbital stabilisation should also be present in o-dithiins, but the differences in reactivity between the two isomers would not then be adequately explained.

There was some doubt among earlier workers that the disulphide existed as the 8 π -electron o-dithiin (2) at all. The alternative structure was the acyclic dithioaldehyde, 6.



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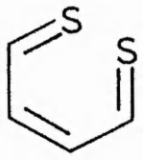


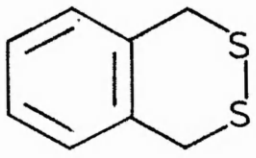
(6)

The o-dithiin structure (2) was confirmed by Fabian[10,11] and co-workers, who carried out molecular orbital calculations and found good agreement between the experimentally observed [$\pi \rightarrow \pi^*$] transition absorption (451 nm) and the calculated value (439 nm) for 2 (the calculated absorptions for 6 are 376 nm[$\pi \rightarrow \pi^*$] and 762 nm [$n \rightarrow \pi^*$]).

The same conclusion was arrived at by Geiseler[12], who determined the enthalpy of combustion and hence the enthalpy of formation for 3,6-diphenyl-o-dithiin.

An evaluation of the esr spectra obtained from the cation radicals[13] produced when dibenzo[c,e]-o-dithiin was oxidised with concentrated sulphuric acid indicated that the unpaired electron was largely localised on one of the sulphur atoms.

As is the case for anhydro-o-dithiins, there are few references to dihydro-o-dithiins in the literature. Benzo[d]-o-dithiins such as 7 are more frequently encountered[14], and the parent unsubstituted 3,6-dihydro-o-dithiin (8) has been isolated[15], although the substance polymerises readily.



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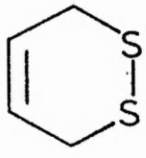
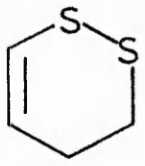
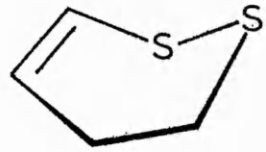


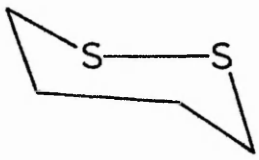
(8) $\theta \sim 90°$

The reactivity of cyclic disulphides has been quantitatively correlated[16] with their C-S-S-C dihedral angle (Θ); that in both 7 and 8 is approximately 90^{o} (deduced from models) and this may well account for the greater stability of these systems, relative to the unknown 3,4-dihydro-o-dithiin (9), which would have $\Theta \sim 75^{o}$. o-Dithian (10), o-dithiolan (11) and o-dithiole (12) have Θ values of 60^{o}, 25^{o} and 0^{o} respectively, and an increase in reactivity parallels the decrease in Θ.

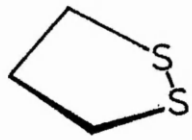


(9)
$\Theta \sim 75°$

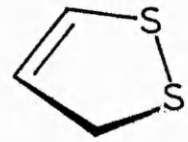




(10)
$\Theta \sim 60°$



(11)
$\Theta \sim 25°$



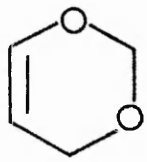
(12)
$\Theta \sim 0°$

As would be expected, the dithiins 7 and 8, which have half-chair conformations, invert[14] faster than o-dithian (10); this was shown by the low temperature nmr non-equivalence points for the α-methylene protons.

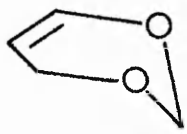
Not surprisingly, no examples of o-dioxiins are known, although a few 3,6-dihydro-o-dioxins have been obtained[17] by the photochemical reaction of oxygen with suitable dienes. The product cyclic peroxides are highly

unstable and tend to explode when heated.

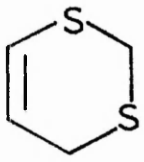
As is the case with their sulphur counterparts, p-dioxins are comparatively well known[18,19], and are found to be more stable than the corresponding divinyl ethers. m-Dioxins[20,21] on the other hand, are much more reactive, and have been compared[22] in reactivity to ketenes. The parent unsubstituted m-dioxin (13), which was isolated in 1964[23], boils at 78° and exists in a half-chair or 'envelope' conformation.



(13)



Although m-dithiins might be expected to be more stable than m-dioxins, they are scarcely better known, and few reports of their properties are available. Models suggest that m-dithiin (3) might be expected to adopt a half-chair conformation. X-ray studies of representative molecules carried out for the author (see pages 37 and 46) show that these predictions are essentially correct.



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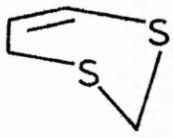
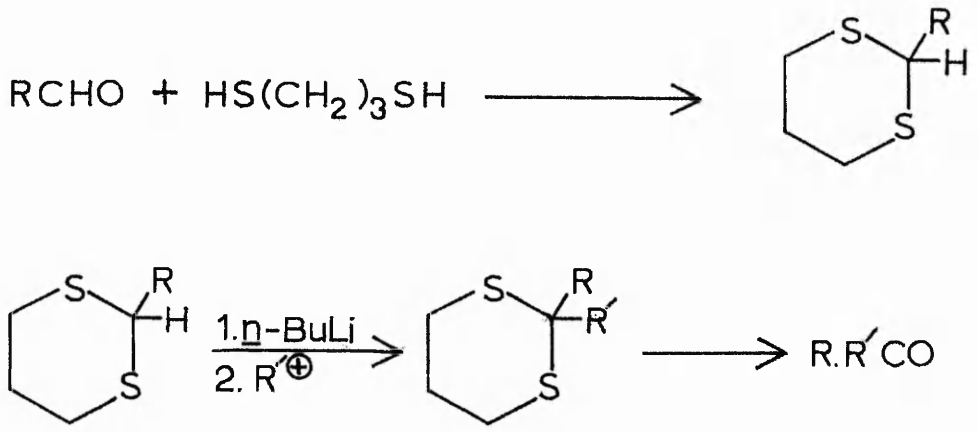


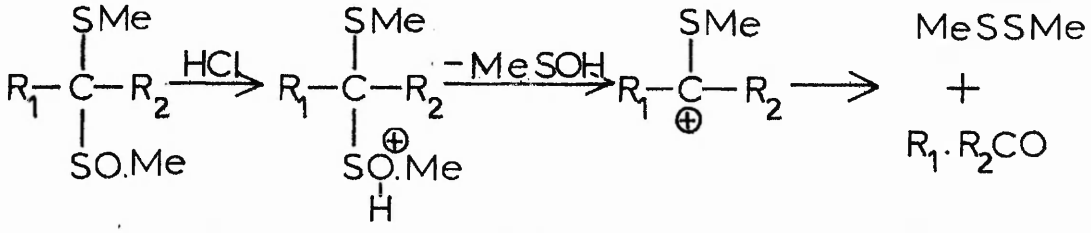
Since m-dithiins are cyclic thioacetals, they can be expected to undergo characteristic reactions; for example, proton abstraction[24] and dethioacetalisation[25-28]. Much of the work in this area has centred on the use of m-dithiane as a masked acyl carbanion equivalent[29,30] (see

scheme), and the analogous reactions on unsaturated cyclic



thioacetals such as m-dithiins are rare.

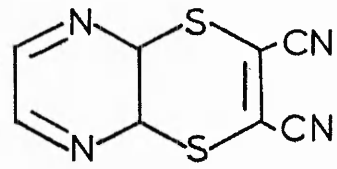
A specific type of thioacetal hydrolysis which may be applicable to m-dithiins[31], is that reported to occur on treatment of thioacetal monosulphoxides with hydrogen chloride. The mechanism of this reaction is unclear, but the authors[32] postulate the intermediacy of the α-thiocarbocation shown in the following sequence.



Heterocycles containing two sulphur atoms show a wide range of physiological activity, and this is illustrated by the following examples from the recent literature. The 5,6-dihydro-p-dithiin derivatives, 14, have sedative[33], muscle relaxant[34], insecticidal and acaricidal[35] properties and compounds related to cyano-p-dithiins such as 15, show fungicidal, algicidal and

bactericidal[36] activity. Several sulphoxides (eg. 16[37], 17[38] and 18[39]) and sulphonium salts (eg. 18[38], 19[40] and 20[41]) have plant growth regulatory or fungicidal activity and sulphones such as 21 are herbicides, desiccants and defoliants[42].

(14)



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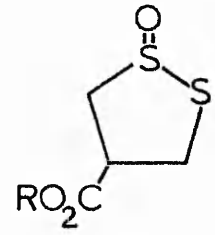

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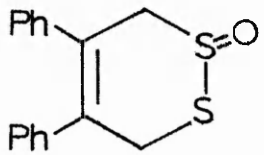

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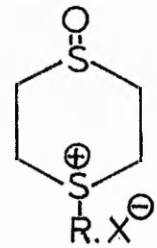

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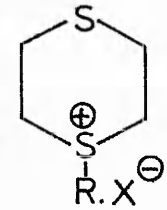

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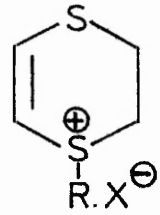

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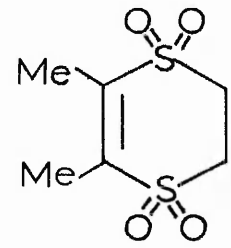


(21)

X = BF_4

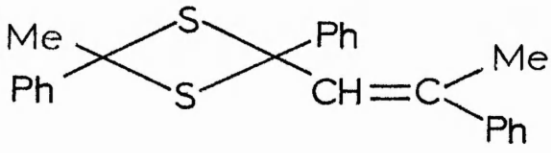
R, R' = alkyl

In view of the activity outlined above of some of these p-dithiins, there is an obvious interest in the preparation of some of their m- and o-dithiin analogues.

m-DITHIINS

PART 1. INTRODUCTION

In 1895, Baumann and Fromm[43] treated acetophenone with hydrogen sulphide in the presence of hydrochloric acid. As well as the expected trimer, 2,4,6-trimethyl-2,4,6-triphenyl-1,3,5-trithiane, they isolated a second crystalline product which was called 'anhydrotriacetophenone disulphide'. The two possible structures suggested for the product were the dithietane, 22, and the m-dithiin, 23, the latter being preferred.



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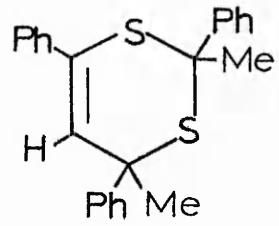
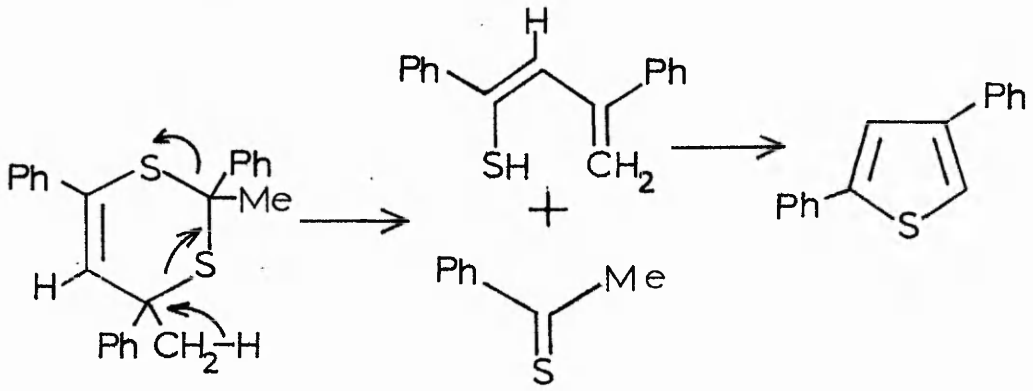


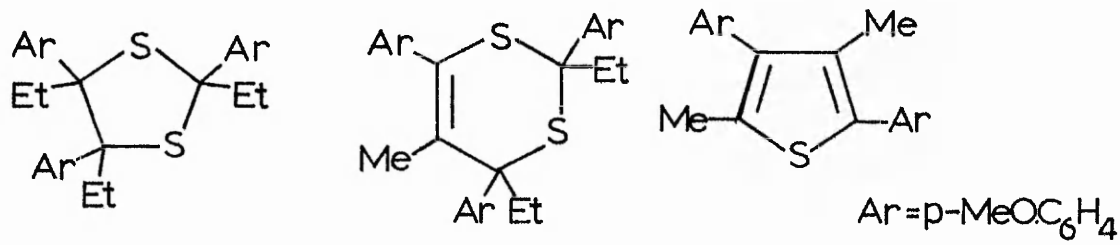
(23)

Pyrolysis of the disulphide at 180° gave a blue liquid, presumably thioacetophenone, and further heating resulted in the evolution of hydrogen sulphide and the formation of styrene and 2,4-diphenylthiophen. Campaigne, on repeating this work in 1944[44], could neither confirm the m-dithiin structure (23) for the disulphide, nor reproduce the pyrolysis results using the same conditions; only a trace of 2,4-diphenylthiophen was obtained. He did, however, obtain an 83% yield of 2,4-diphenylthiophen when the thermal reaction was carried out in refluxing xylene in the presence of copper chromite. The following

course for the reaction was proposed:



Previously, Linnell and Sharma[45] had treated p-methoxypropiophenone with hydrogen sulphide in the presence of hydrochloric acid, and had assigned the structure, 2,4,5-tri-p-anisyl-2,4,5-triethyl-1,3-dithiolane (24) to the product, although no proof was given. This work was repeated by Campaigne[44], who proposed the m-dithiin structure, 25, by analogy with the results of Baumann and Fromm[43]. Pyrolysis of the product in the presence of copper chromite led to the



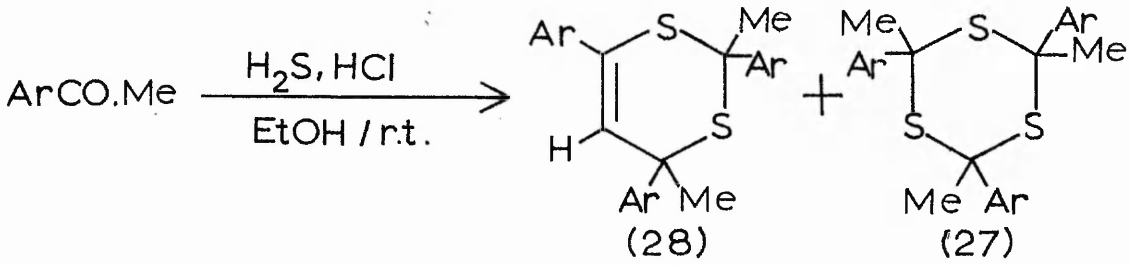
(24) (25) (26)

isolation of 2,4-di-p-anisyl-3,5-dimethylthiophen (26).

The m-dithiin structure (23) for the 'anhydrotriacetophenone disulphide' was finally confirmed

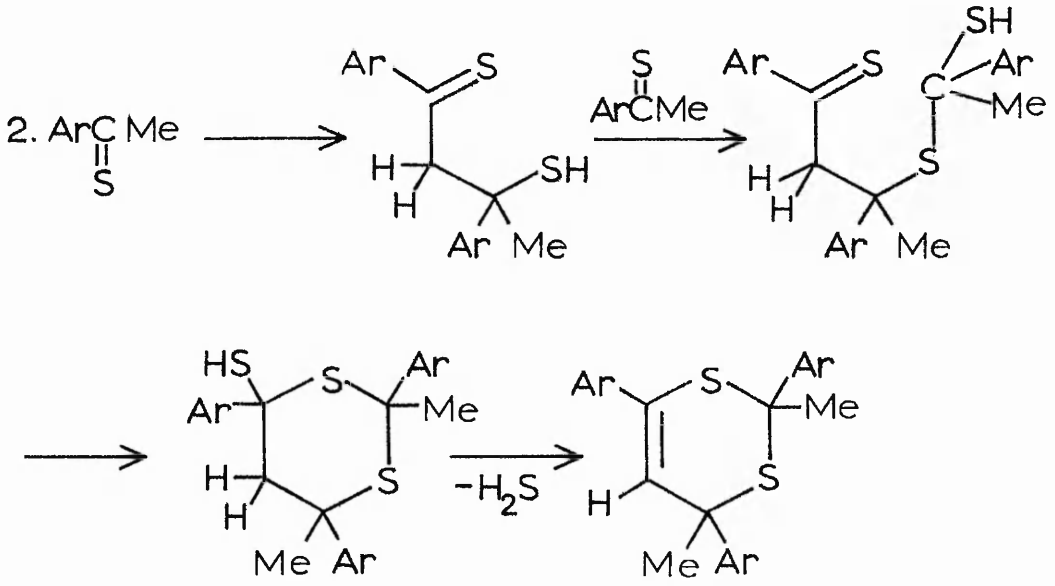
in 1962 by Pasto and Servé[46], who found that the ^{1}Hnmr spectrum was consistent with 23 and not with 22. Furthermore, ozonolysis yielded benzoic acid and not acetophenone (which would have been expected from 22).

Campaigne, Reid and Pera[47] applied the hydrogen sulphide-hydrogen chloride reaction to a series of aryl ketones. These authors made the interesting observation that the product composition varied with the temperature of the reaction; at 0-5°, the trithianes 27a-e predominated, whilst at room temperature, the m-dithiins 28a-e were the major products.

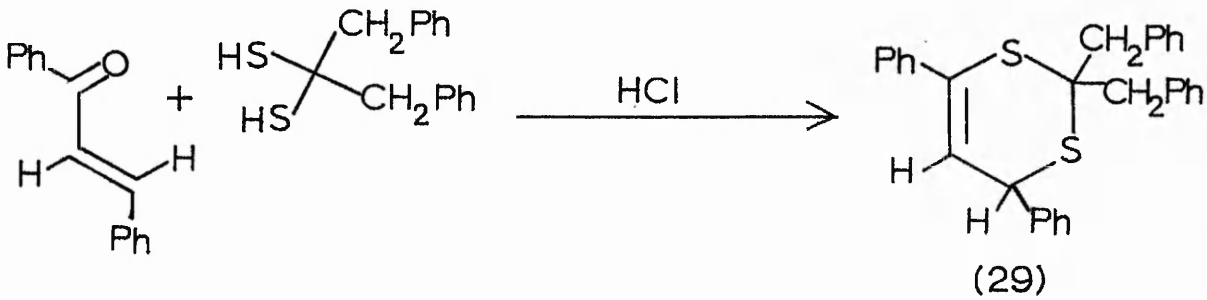


a. Ar = p-F.C_6H_4
b. Ar = p-Cl.C_6H_4
c. Ar = p-Br.C_6H_4
d. Ar = p-I.C_6H_4
e. Ar = p-Ph.C_6H_4

The reaction sequence depicted below was suggested by Breslow and Skolnik[48], although no supporting experimental evidence was presented.



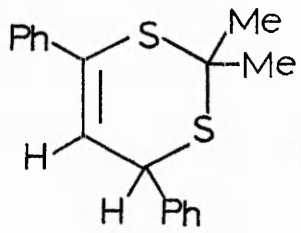
In an alternative approach to the m-dithiin system, a geminal dithiol is reacted with an $\alpha\beta$ -unsaturated ketone. An example of such a reaction was reported by Campaigne and Edwards[49], who prepared the m-dithiin 29 by the reaction of 1,3-diphenylpropane-2,2-dithiol with benzylideneacetophenone (chalcone) in ethanolic hydrogen chloride. The identity of the product was established by ^{1}Hnmr and elemental analysis.



(29)

This type of reaction was also used by Demuynck, Prudhomme and Thuillier[50] in 1966 who treated 2,2-propanedithiol with benzylideneacetophenone to give 2,2-dimethyl-4,6-diphenyl-m-dithiin (30). Again, ^{1}Hnmr

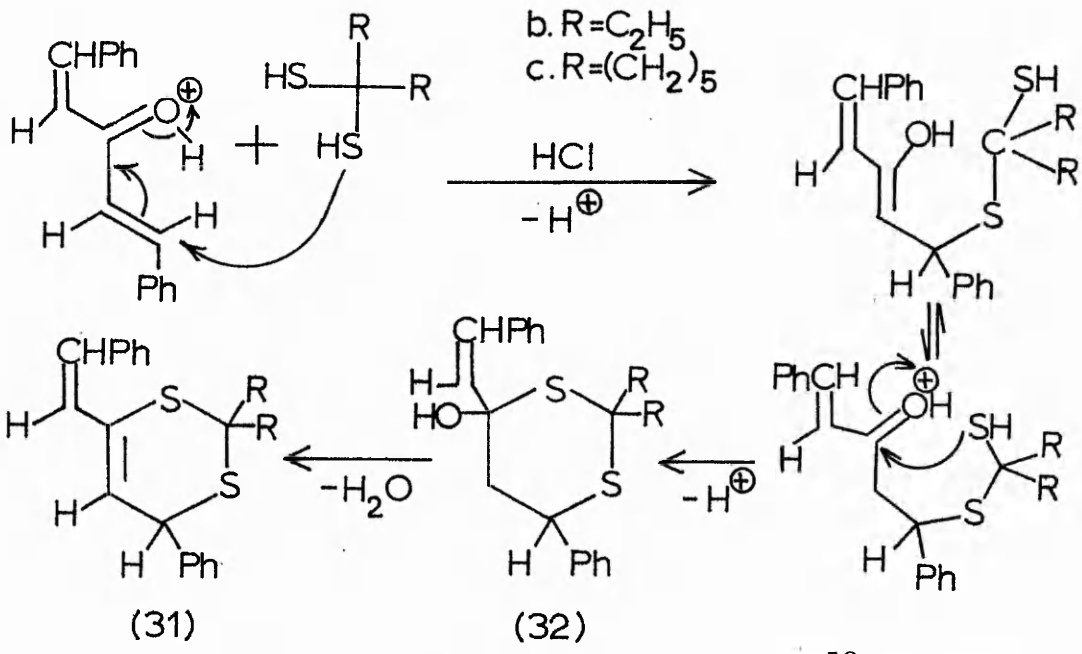
spectroscopy provided the main evidence for the structural assignment.



(30)

The same workers found that the appropriate dithiols reacted in a similar fashion with one equivalent of dibenzylideneacetone to give the m-dithiins 31a-c; the following reaction mechanism seems likely.

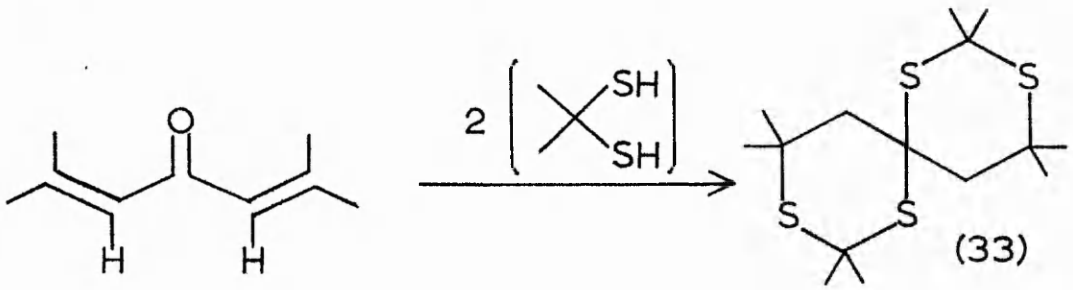
a. R=Me
b. R=C_2H_5
c. R=$(CH_2)_5$



(31) (32)

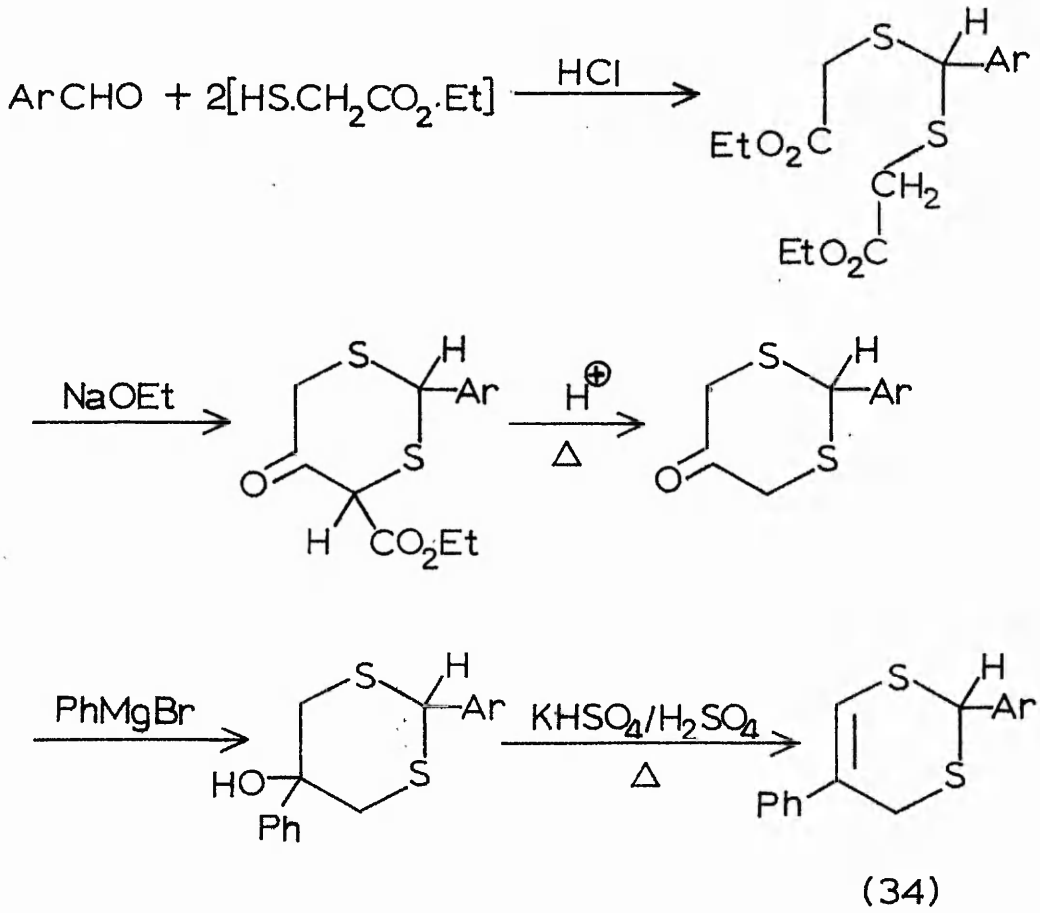
Diisopropylideneacetone was found[50] to react with two molar equivalents of 2,2-propanedithiol to give the unusual spirodithiane, 33. It was proposed that the reaction followed a similar course to that described above to the point where the tertiary alcohol, 32, was formed. In this case, however, the simple dehydration process was

replaced by a further reaction with the dithiol.



(33)

In the first rational approach to m-dithiins, Lüttringhaus and co-workers[51] synthesised 34a and b by the sequence of reactions shown below.

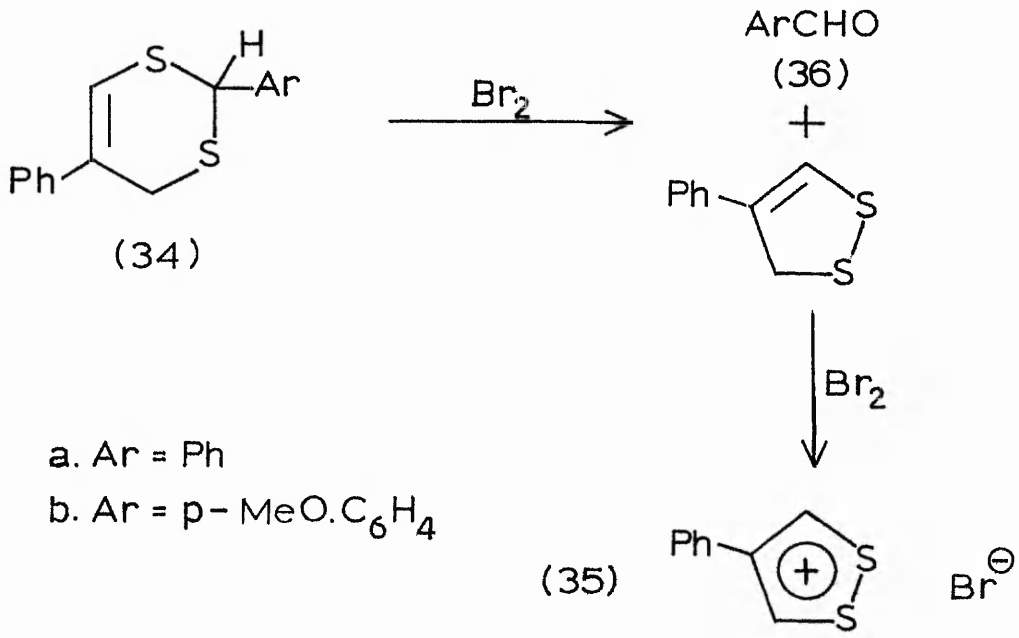


(34)

a. Ar = Ph

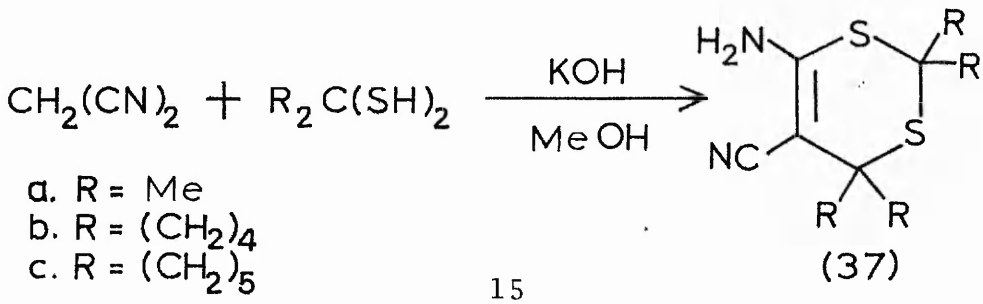
b. Ar = p-MeO.C_6H_4

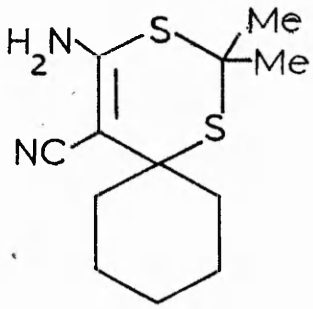
The m-dithiins 34a and b were shown[52] to react with bromine in acetic acid to form 4-phenyl-1,2-dithiolium bromide (35), together with the aldehydes 36a and b.



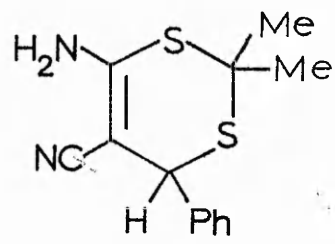
Treatment of m-dithiins 34a and b with sulphuryl chloride followed by perchloric acid gave the corresponding dithiolium perchlorates in 40% yield.

Jentzsch and Mayer[53] prepared the 6-amino-5-cyano m-dithiins 37a-c by the reaction of geminal dithiols with malononitrile in methanol containing a little potassium hydroxide.





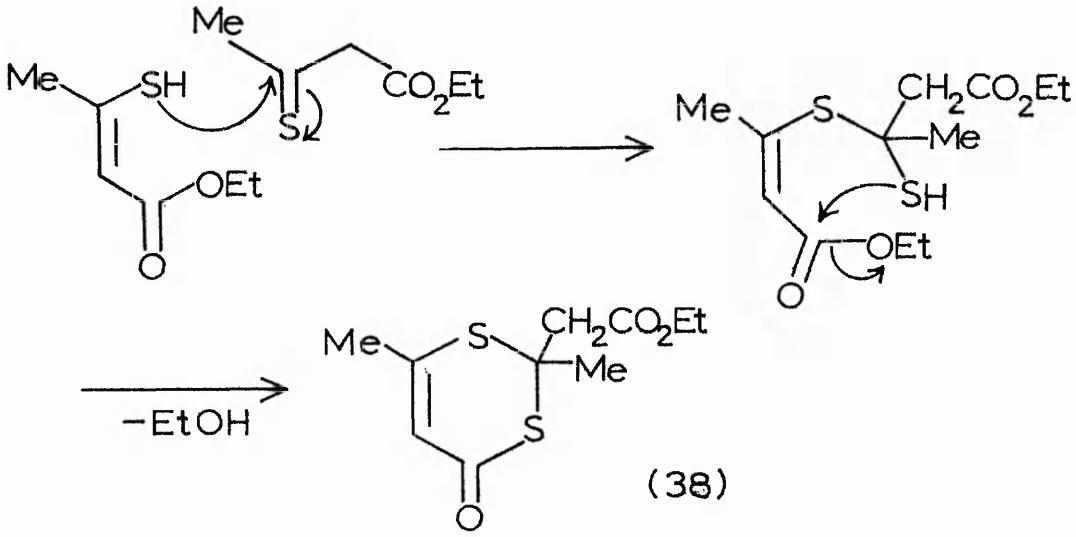
(37d)



(37e)

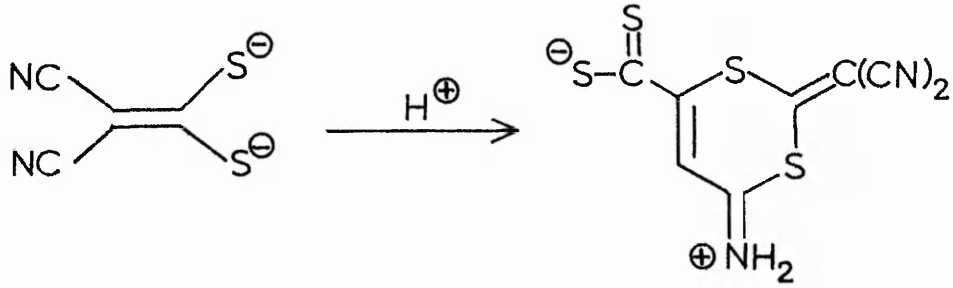
Despite the electron withdrawing effect of the nitrile on the amino function, m-dithiins 37a-c were sufficiently basic to permit N-acetylation and Schiff base formation. Analogous m-dithiins 37d and e were obtained if the malononitrile was replaced by cyclohexylidenemalononitrile or benzylidenemalononitrile.

Duus and Lawesson[54] treated ethyl acetoacetate in ethanolic hydrogen chloride with hydrogen sulphide at 0^{o}. Three products (in addition to the expected ethyl thioacetoacetate) were isolated, and one of these was identified by its spectroscopic properties as 2,6-dimethyl-2-ethoxycarbonylmethyl-m-dithiin-4-one, (38). The proposed mechanism for the formation of 38 involved the dimerisation of ethyl thioacetoacetate and subsequent elimination of ethanol.

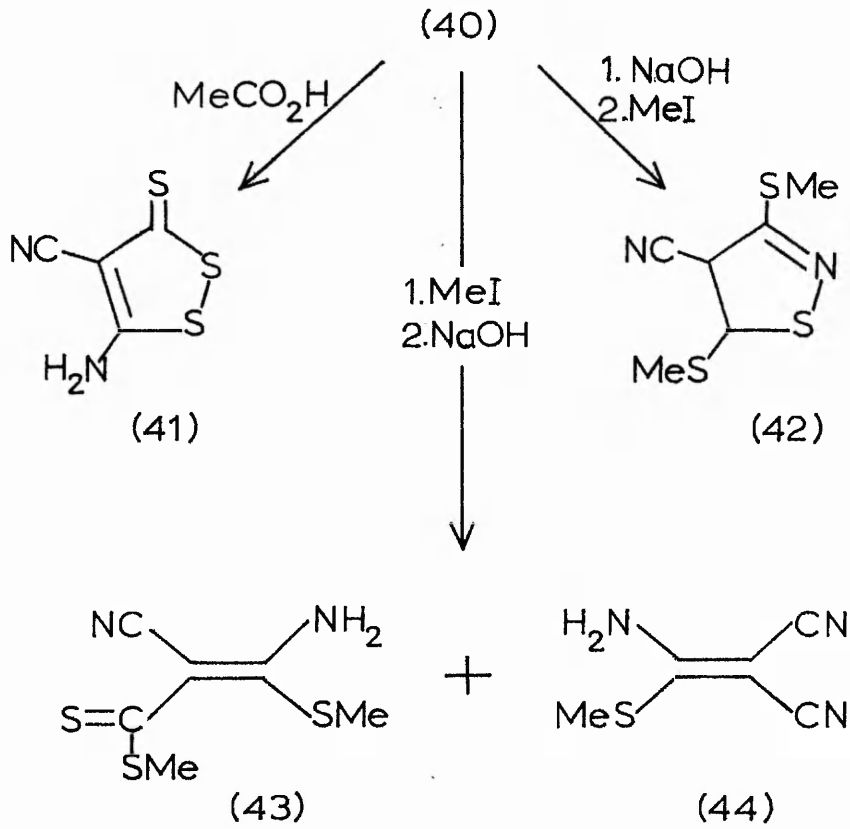


(38)

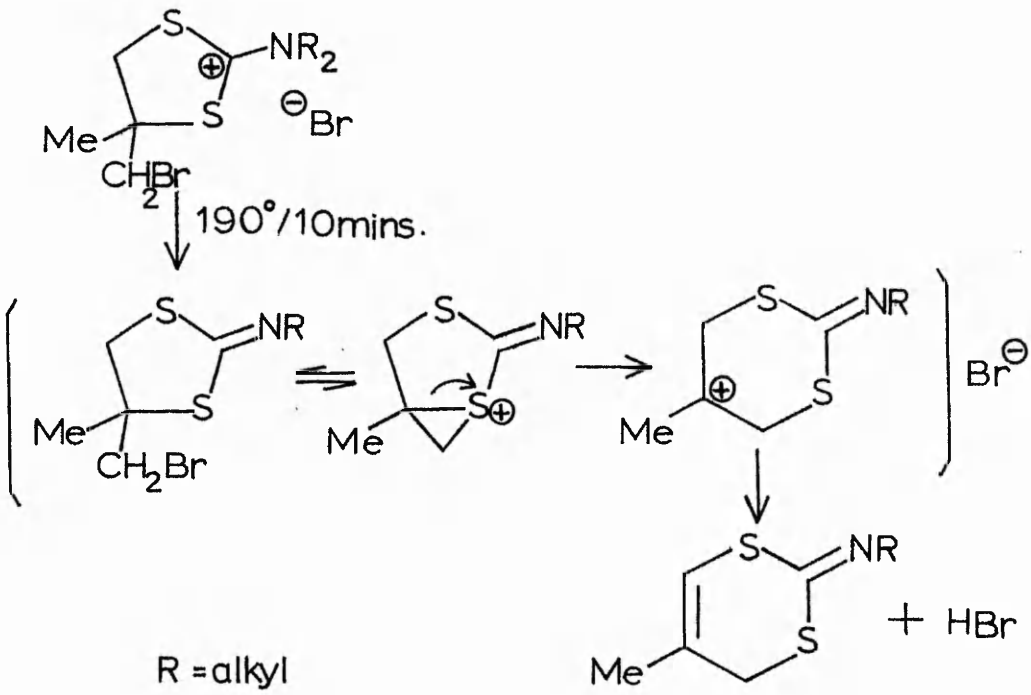
The isolation of the unusual m-dithiin, 40, has been reported by Gewald[55], who reacted the dithio-salt, 39, with acid. The m-dithiin was rather labile; with acid it formed the 1,2-dithiole-thione, 41, and on treatment with alkali followed by methyl iodide, it formed the isothiazole, 42. Reaction with methyl iodide followed by alkali, however, gave the open-chain products 43 and 44. The mechanism for the formation of 40 has not been elucidated.



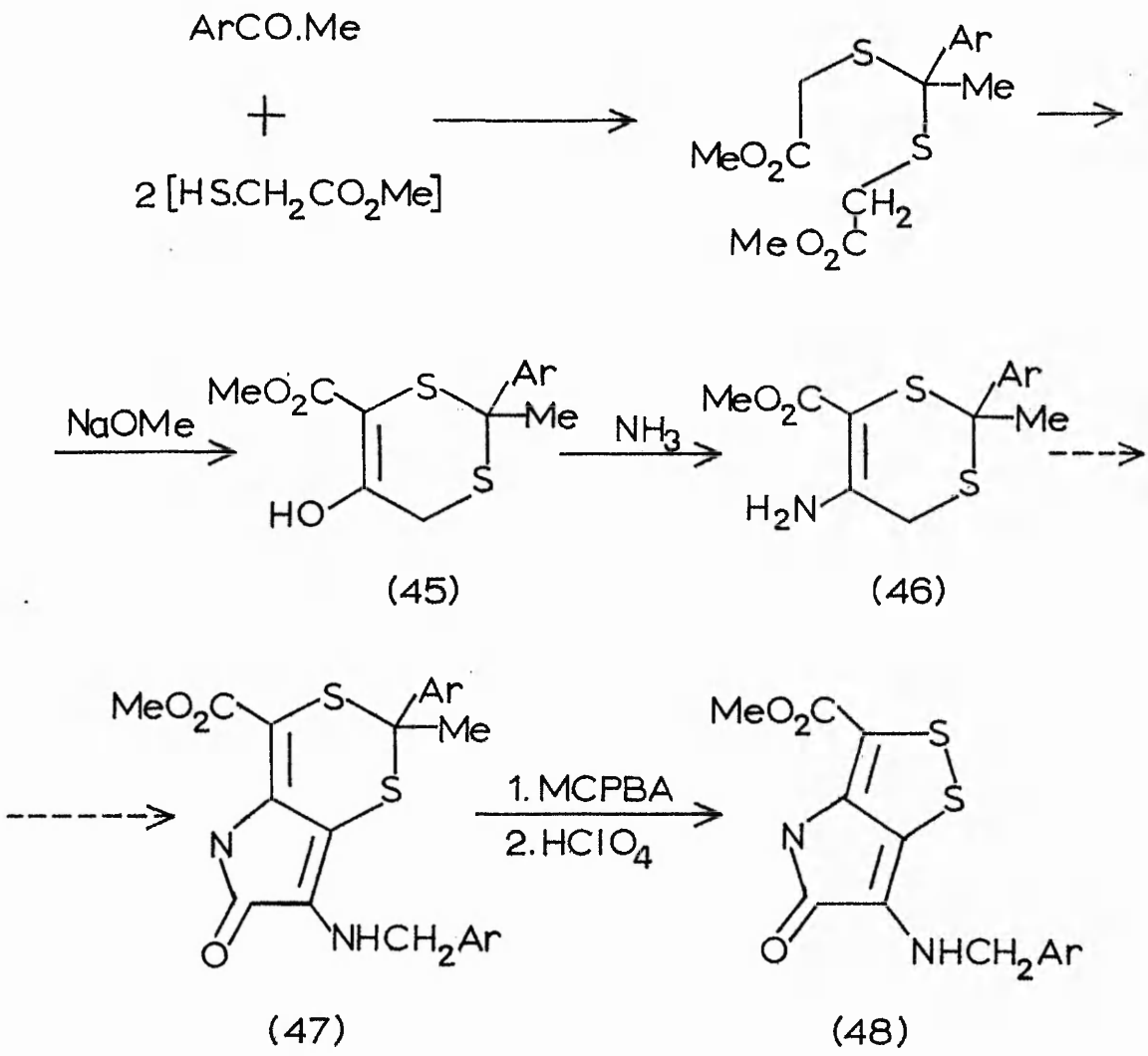
(39) (40)



p-Dithiins have frequently been prepared by the ring expansion of 1,3-dithiolium salts[56,57]. The only m-dithiin to be produced in this fashion was reported by Hiratani et al[58], and the proposed mechanism involves the formation of an episulfonium intermediate:



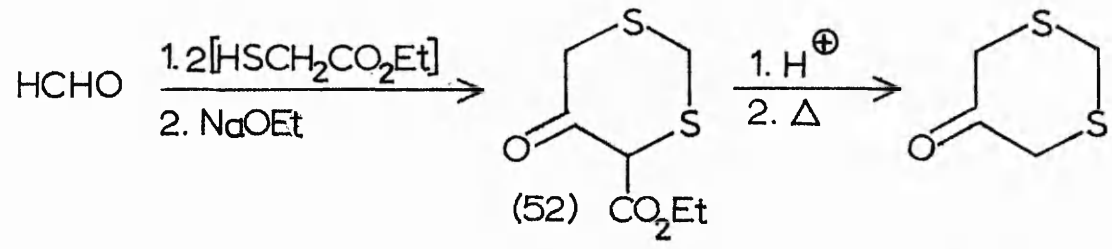
The m-dithiins 45 and 46 were prepared by Ellis and co-workers[31] during the total synthesis of the antibiotic holomycin. (c.f. Lüttringhaus and Prinzbach[51]; page 14) In a later stage of the synthesis, the fused m-dithiin, 47, underwent ring contraction[59] to the dithiole 48 when treated with m-chloroperbenzoic acid (MCPBA) and perchloric acid.

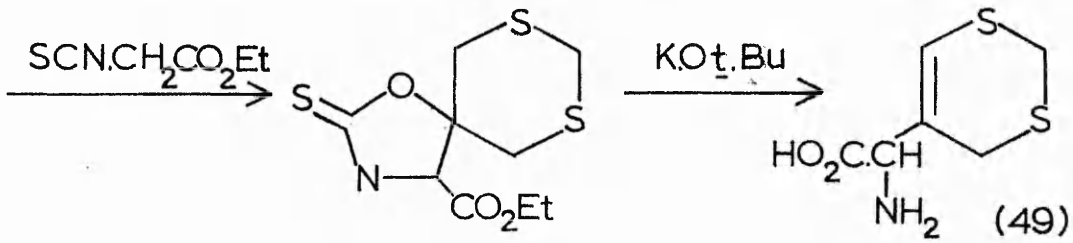


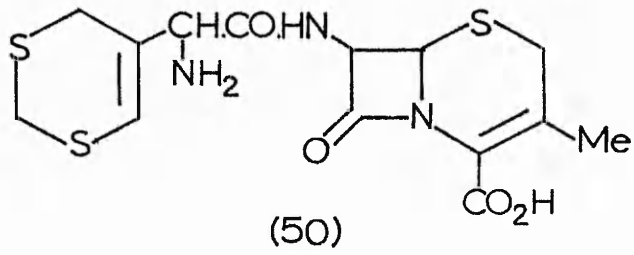
Ar = p-MeO.C_6H_4

The ring contraction probably involves the intermediate formation of a sulphoxide at the 3 position in m-dithiin 47 and is therefore comparable with the dethioacetalisation procedure outlined on page 7.

Amino-acid, 49, has recently found use[60] as a substituent in the deacetoxy cephalosporin, 50; it is prepared as illustrated below.

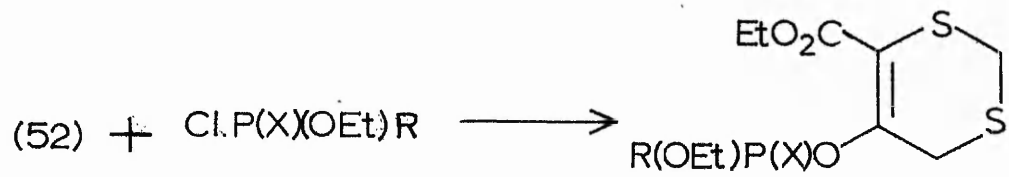






(50)

The m-dithiin, 51, which is also prepared via the Dieckmann condensation product, 52, has been employed[61] as an insecticide.

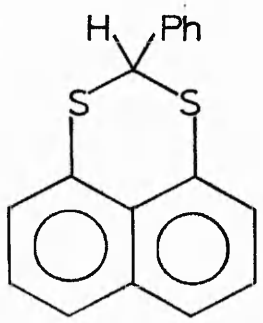


X = O ; R = OEt

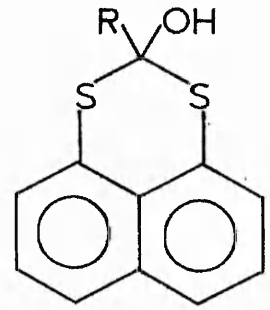
X = S ; R = OEt, Et, Ph

(51)

Several fused m-dithiins have been prepared. They include 1,8-dithianaphthalene derivatives such as 53, (prepared by Price and Smiles[62] as early as 1928) 54[63] and 55. The latter compound was transformed[65] by pyrolysis



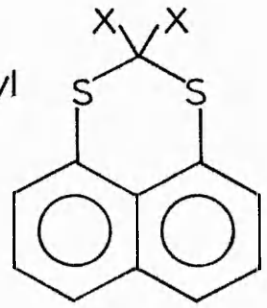
(53)

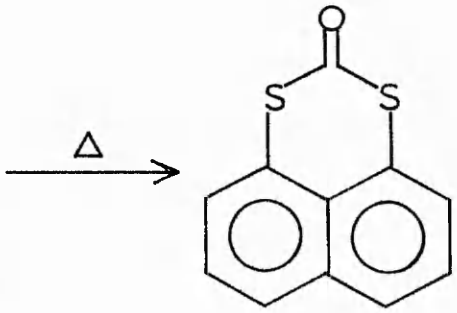


R = Ph or Me

(54)

X=p-tosyl

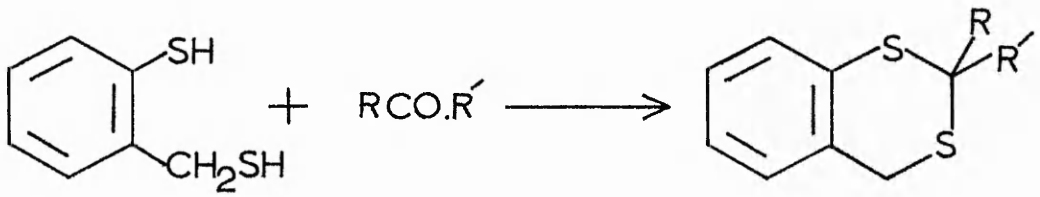




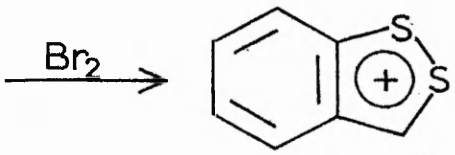
(55) (56)

into the ketone 56.

Lüttringhaus et al[14,52] have synthesised the benzodithiins 57a-c by the reaction of o-mercaptomethylthiophenol with appropriate aldehydes or ketones. On treatment with bromine, these m-dithiins suffered ring contraction to give the dithiolium salt, 58.



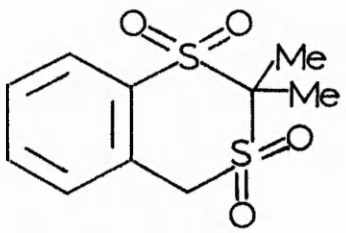
(57)



(58)

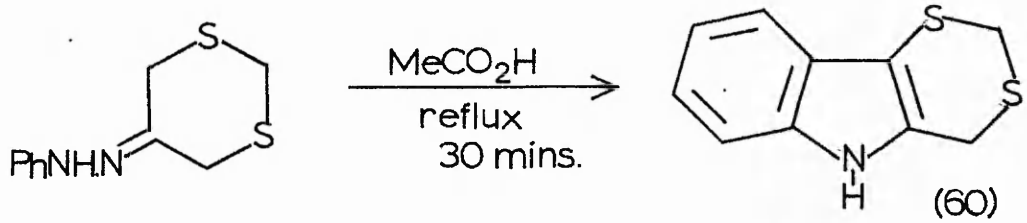
a. R = Ph, R´ = H
b. R = p-MeO.C6H5, R´ = H
c. R = R´ = Me

The disulphone 59 was formed[66] by oxidation of the 2,2-dimethyl-5,6-benzodithiin (57c) with potassium permanganate in acetic acid.

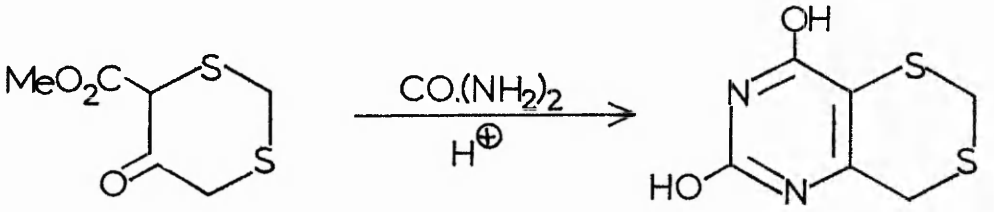


(59)

m-Dithiino-indoles (60) and -pyrimidines (61) have been prepared by Martani[67] by the reactions shown below, the first of which is a type of Fischer indole synthesis.

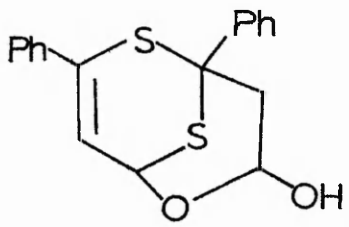


(60)

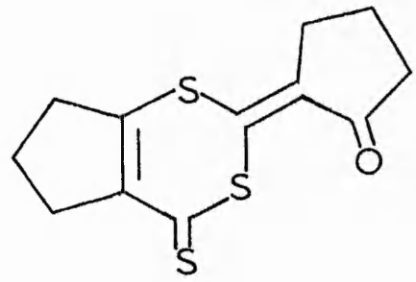


(61)

The more unusual fused m-dithiins 62 and 63 were isolated and identified by Pulst et al[68] and by Takeshima et al[69], respectively.

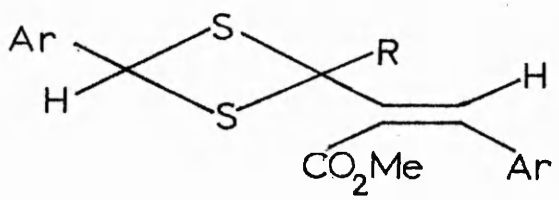


(62)



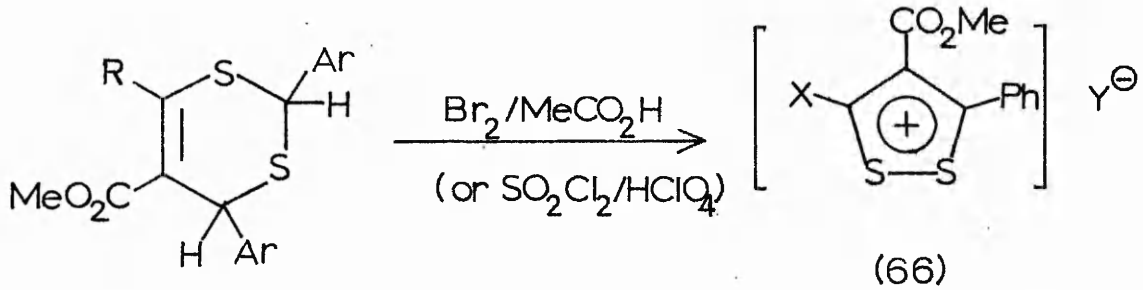
(63)

The first synthesis of a m-dithiin carboxylic acid derivative was reported in 1970 by Eisner and Krishnamurthy[70,71], who reacted aromatic aldehydes with acetylenic esters in the presence of hydrogen sulphide and boron trifluoride etherate. The products, 64a-d, were obtained in good yield, and the possible alternative dithietane structure, 65, was discounted on the basis of the ^{1}Hnmr spectrum of 64b; the lack of an olefinic proton precluded the possibility that the dithietane 65b was present. Ring contraction to the dithiolium salts, 66a-d, with the simultaneous formation of benzaldehyde occurred on treatment with bromine or sulphuryl chloride (c.f. the findings of Lüttringhaus et al, ref. 52), confirming the m-dithiin structure for the compounds 64a-d.



(65)

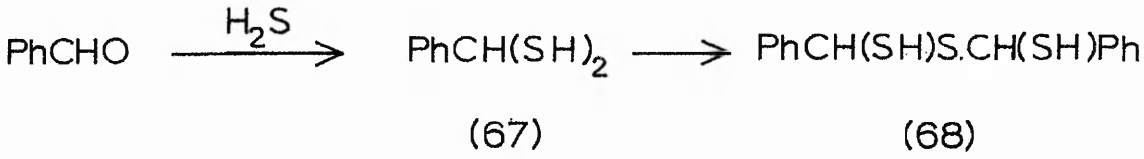
a. R = H , Ar = Ph
b. R = CO_2Me, Ar = Ph
c. R = H , Ar = p-MeC_6H_4
d. R = H , Ar = p-$Cl.C_6H_4$



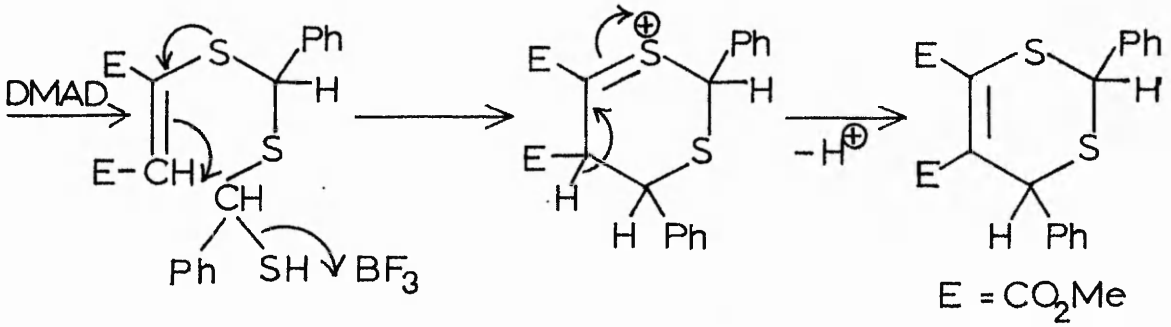
(64)

(66)
a. X = H, Y = ClO_4
b. X = H, Y = Br
c. X = CO_2Me, Y = ClO_4
d. X = CO_2Me, Y = Br

The proposed mechanism for the formation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (64b) is shown below. It was visualised as proceeding via the geminal dithiol 67 which undergoes self condensation to form 68; nucleophilic addition to the acetylenic ester is then followed by cyclisation.



(67) (68)

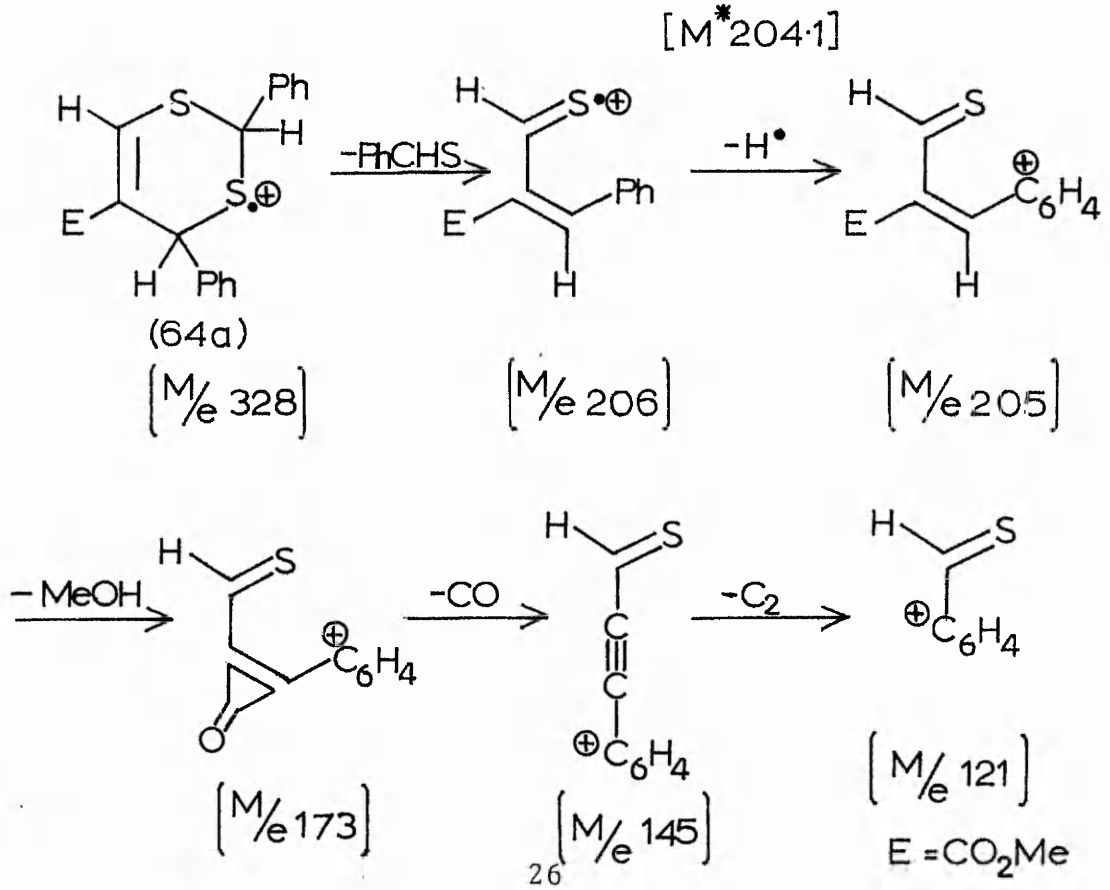


$E = CO_2Me$

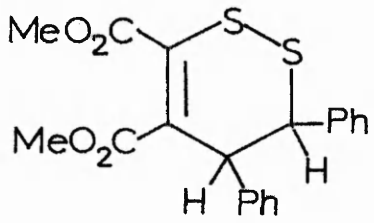
DMAD = dimethyl acetylene-dicarboxylate

It was observed that improved yields of the m-dithiin were obtained when 2,4,6-triaryl-1,3,5-trithianes were used in place of aromatic aldehydes and hydrogen sulphide and that no m-dithiin formation took place when aliphatic aldehydes were used.

The mass spectral fragmentation of m-dithiins 64a-d was found to take place without skeletal re-arrangement, and followed a general pattern. Of particular interest was the observation that the molecular ion loses ArCHS by a reverse Diels-Alder process followed by loss of a hydrogen atom from the resulting odd-electron ion. This is illustrated below for 64a, in which this fragmentation is confirmed by the presence of a metastable peak (m*); further fragmentation involves loss of methanol, carbon monoxide and a C_2 species.



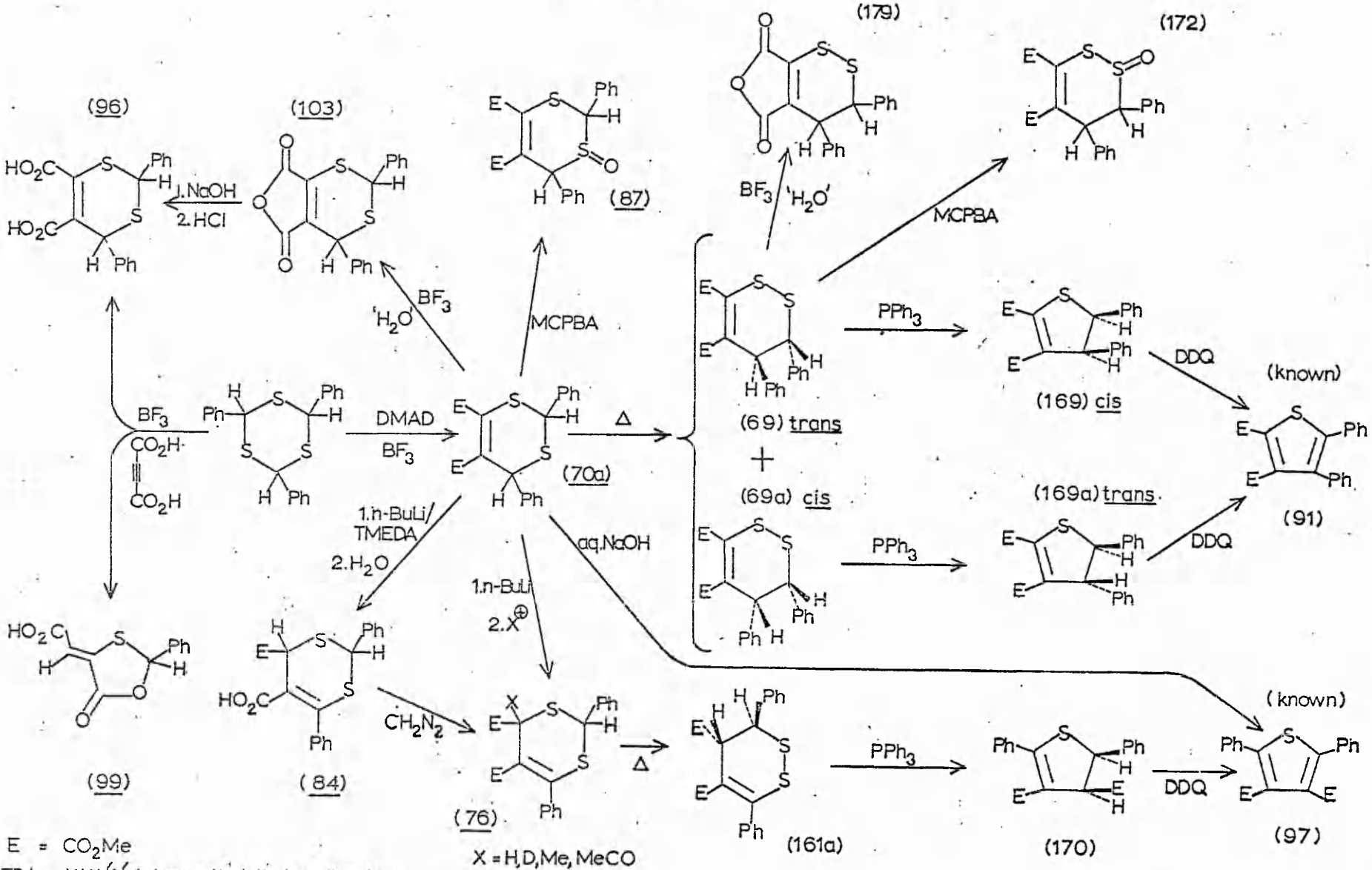
Although some preliminary experiments were carried out[70], little is known of the chemistry of these m-dithiin carboxylic acid derivatives. It was discovered, however, that when m-dithiin 64b was heated briefly at 190° a novel rearrangement took place, resulting in the almost quantitative production of the o-dithiin 69. A radical mechanism for this reaction was proposed (see page122), but no supporting evidence was given.



(69)

The work outlined above revealed the need for further exploration in this area, both in the determination of the chemical properties of these compounds, and in the elucidation of some of the mechanisms by which they react and are formed. The present work aims to fulfil this need, providing at the same time, new compounds for biological testing and evaluation. The series of reactions outlined in Scheme 1 represent the framework of this study, and were reported by the author in 1980[73]. A detailed discussion of this work is presented in the following sections.

SCHEME 1

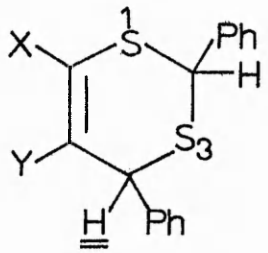

(96)
(103)
(87)
(179)
(172)
1.NaOH
2.HCl
BF3
'H2O'
MCPBA
DMAD
BF3
Δ
(70a)
(69) trans
+
(69a) cis
PPh3
(169) cis
(169a) trans
DDQ
(known)
(91)
aq.NaOH
1.n-BuLi/
TMEDA
2.H2O
1.n-BuLi
2.X⊕
CH2N2
(99)
(84)
(76)
X = H,D,Me,MeCO
(161a)
(170)
(97)
E = CO2Me
TMEDA = N,N,N',N'-tetramethylethylenediamine
DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone
MCPBA = 3-chloroperbenzoic acid

PART 2. DISCUSSION

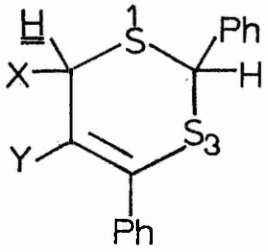
A note on nomenclature

Substituted m-dithiins such as those shown below can exist as tautomers. Throughout this study these will be distinguished by reference to the position of the allylic ring proton.

e.g.



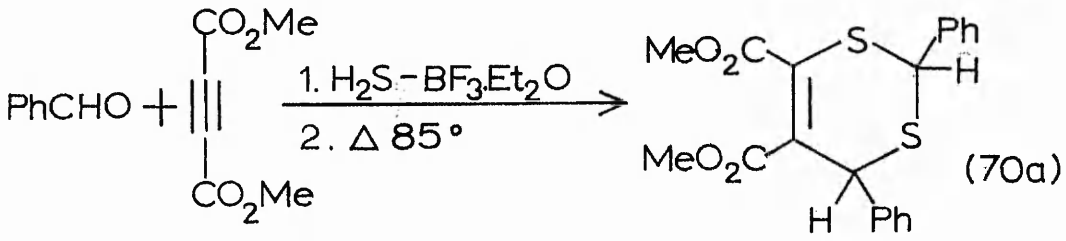
------2,4-diphenyl-4H-m-dithiin------



-------2,4-diphenyl-6H-m-dithiin-------

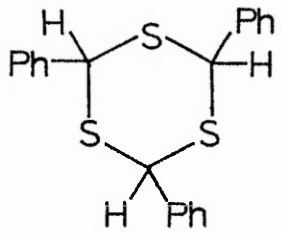
1. Preparation of m-Dithiins

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was prepared using the original method of Eisner and Krishnamurthy[70,71]. This involved the passage of hydrogen sulphide gas through a solution of benzaldehyde in benzene containing boron trifluoride etherate and two equivalents of dimethyl acetylenedicarboxylate (DMAD).



(70a)

Many variations in the reaction conditions were investigated in order to achieve the reported yield of 'around 100%', but the best that could be achieved was 55%. 2,4,6-Triphenyl-1,3,5-trithiane (71) precipitated during the passage of the hydrogen sulphide, and the final yield of m-dithiin was improved when the trithiane was isolated, purified, and used in place of benzaldehyde and hydrogen sulphide.



(71)

It was found that refluxing benzene could be replaced by toluene in the reaction without adverse effects, provided that the temperature was carefully controlled at 85°C. At higher temperatures (e.g. 95°) the reaction mixture became more complex and the yield was reduced;

below 80° the trithiane failed to react.

Several other catalysts were tried as alternatives to boron trifluoride etherate. These included other Lewis acids such as aluminium (III) chloride or zinc chloride, and proton acids such as p-toluenesulphonic acid. With the exception of aluminium (III) chloride (which was too vigorous, causing side-reactions and giving mixtures of products) these catalysts were somewhat ineffective. The reaction times required for significant production of m-dithiin were far in excess of those observed for boron trifluoride, which proved by far to be the best catalyst.

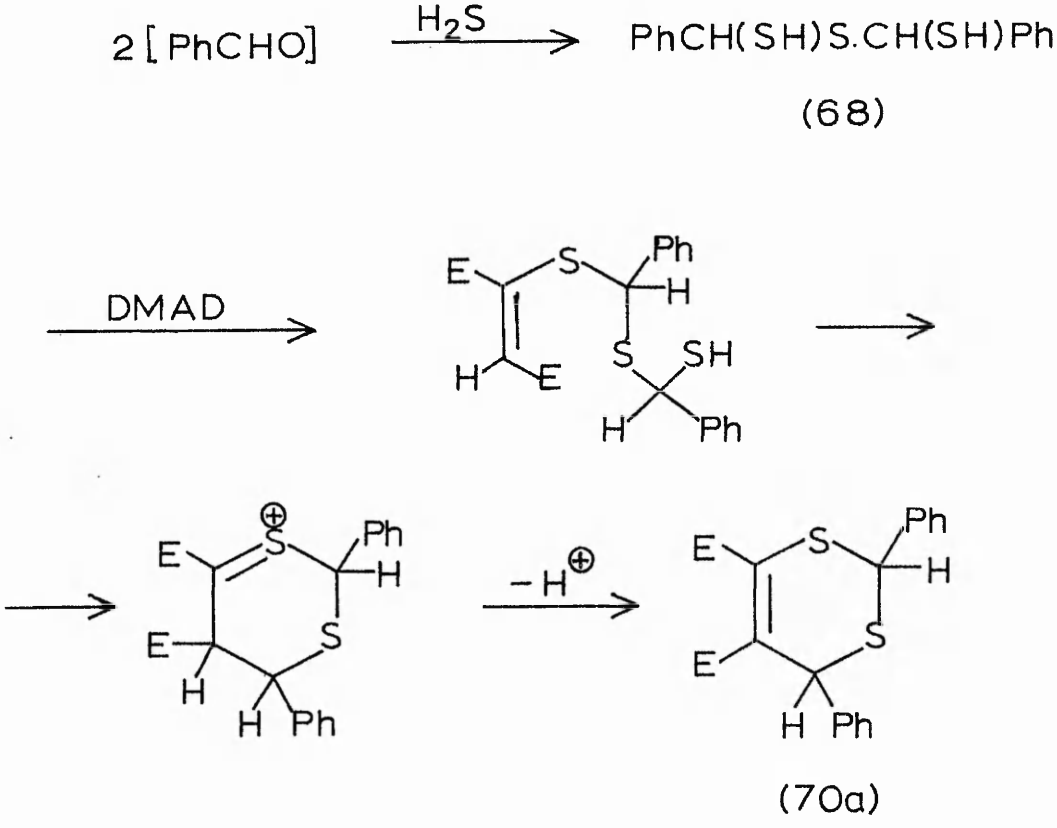
The term 'catalyst' is used very loosely here, because an excess of the boron trifluoride was needed for an efficient reaction. A three-fold excess of the acetylenic ester was also needed; when less than this was employed, the product was contaminated with unchanged trithiane. Since purification by chromatography was impracticable on a large scale, the only viable alternative was fractional crystallisation which was very wasteful. It was essential therefore, to ensure complete reaction by the use of a three-fold excess of the acetylenic ester.

Yields did not suffer significantly if this reaction was carried out on a large scale, but inconvenience was introduced by the low solubility of the trithiane in toluene, which necessitated the use of large volumes of solvent.

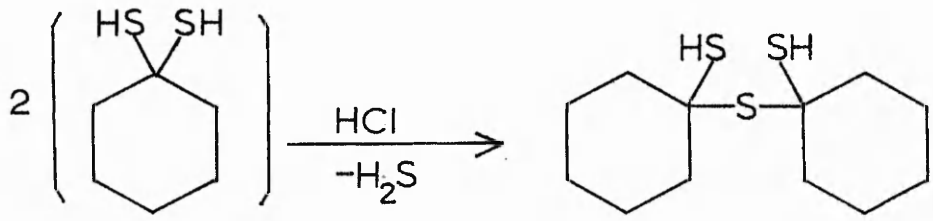
Although many variations and changes in reaction conditions were made, it was concluded that the two main

requirements for a good yield of m-dithiin were firstly the use of pure starting materials (particularly boron trifluoride etherate) and secondly, that the solvent should be anhydrous. With these prerequisites met, yields of pure dry dimethyl 2,4-diphenyl-4H-m-dithiin-5,6,-dicarboxylate (70a) of 70 to 75% were regularly obtained.

At this point, it would seem appropriate to discuss possible mechanisms for the formation of these m-dithiins. It has been proposed[71] that the reaction proceeds according to the following pathway:-



As a precedent for the condensation of a geminal dithiol to an S-bridged dithiol such as 68, the acid induced condensation of cyclohexane-1,1-dithiol (from which the compound 72 was isolated) was cited[72].

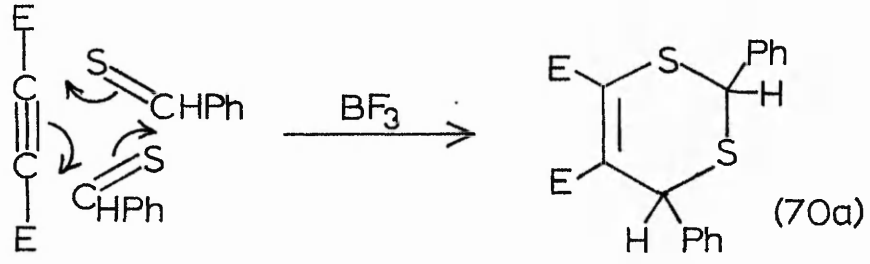


(72)

It is possible that the reaction of benzaldehyde with hydrogen sulphide in the presence of a Lewis acid produces a dithiol similar to 72, but it is apparent that this reacts immediately with more benzaldehyde to give a quantitative yield of 2,4,6-triphenyl-1,3,5-trithiane. Thus the intermediacy of a dithiol in the cyclisation to the m-dithiin seems unlikely.

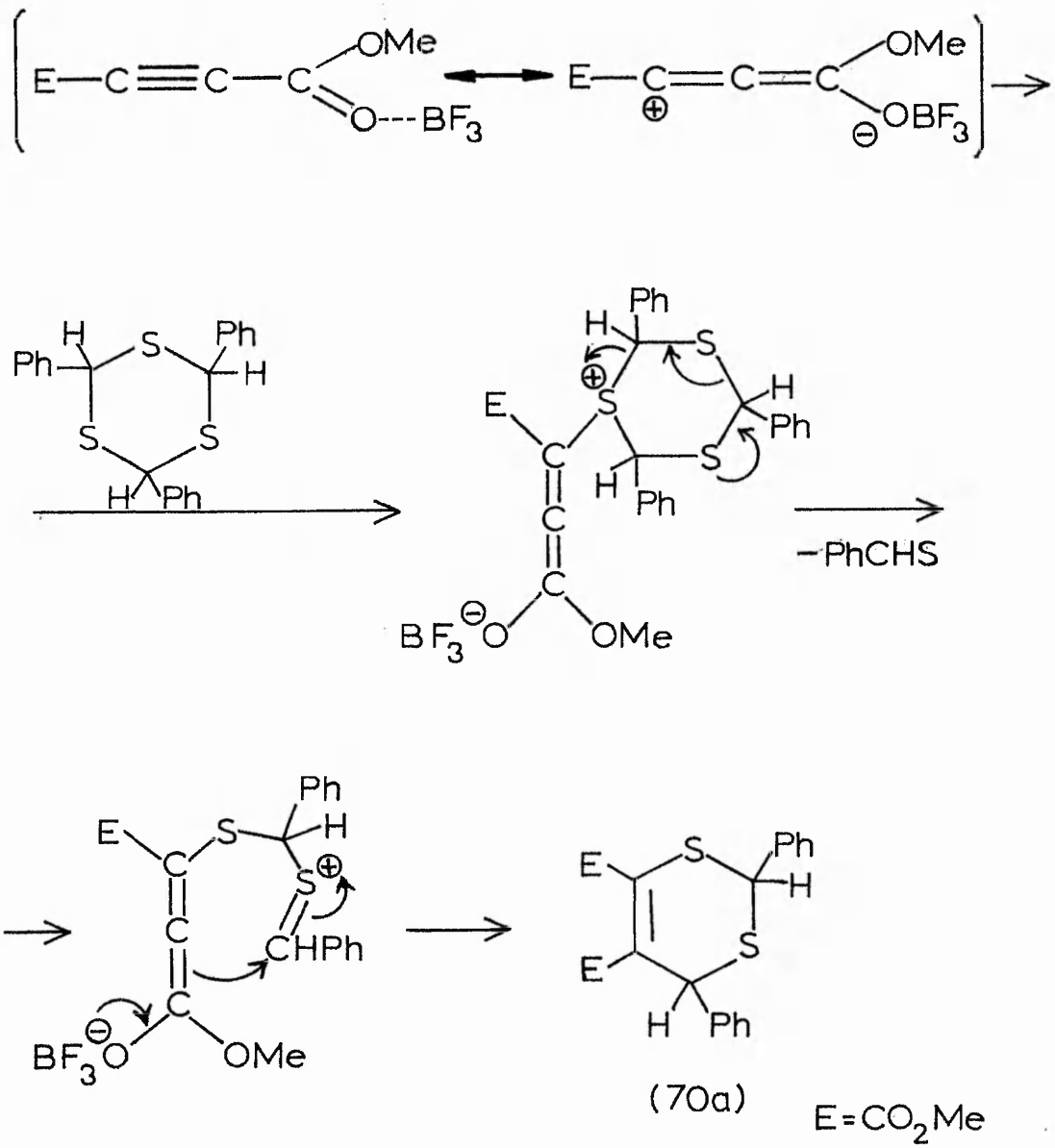
Another mechanism which is possible, but rather unlikely because of the great propensity of thioaldehydes to trimerise, is the concerted cycloaddition of thiobenzaldehyde to DMAD. During the reaction an intense purple colour developed which was probably due to monomeric thiobenzaldehyde. This, however, may be due to just a trace of the thioaldehyde monomer.

$E = CO_2Me$

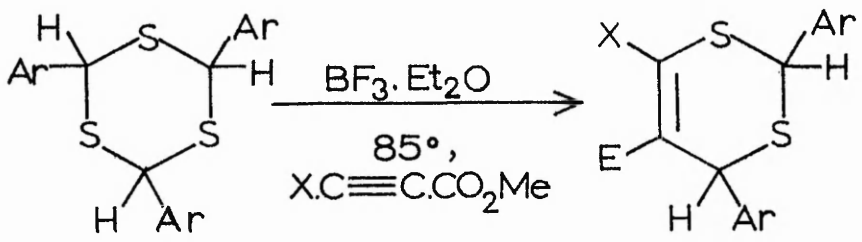


(70a)

An alternative, perhaps more plausible mechanism, which is initiated by the complexation of BF_3 with DMAD is as follows:-



The development work discussed above showed that the best way to obtain m-dithiins of the type 70a is to prepare the trithiane first, then to react it in toluene with DMAD and boron trifluoride etherate. This procedure was employed to synthesise the analogues 70b-e.

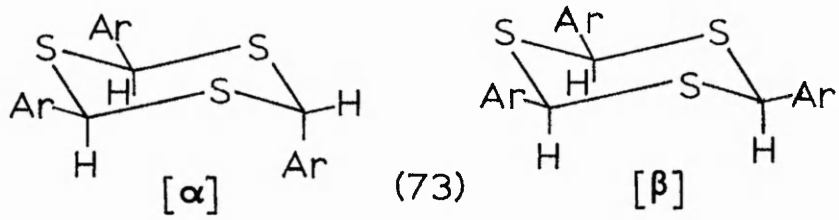


(70)

a. X = CO_2Me, Ar = Ph
b. X = H, Ar = Ph
c. X = CO_2Me, Ar = p-Cl.C_6H_4
d. X = CO_2Me, Ar = p-Me.C_6H_4
e. X = CO_2Me, Ar = p-MeO.C_6H_4

Yields were always significantly lower (30-50%) for the p-substituted analogues 70c-e than for 70a and b (65-75%). It was not possible, however, to correlate these results with the electron donating/accepting ability of the ring substituents. It would have been interesting in this context to look at the reactivity of an aromatic aldehyde bearing a strongly electron withdrawing substituent such as p-nitro. Unfortunately, however, the trithiane in the p-nitro series is almost completely insoluble[74] in the reaction solvent (as well as most other solvents) making it impracticable to use.

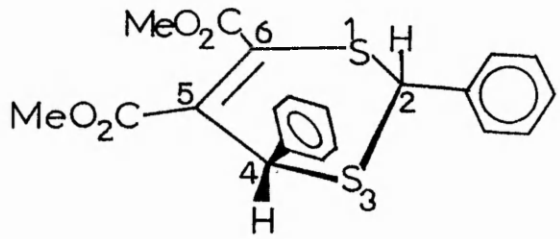
In all cases, a single isomer of the m-dithiin was isolated, regardless of the configuration of the trithiane. Both α and β 2,4,6-tri-p-tolyl- and 2,4,6-tri-p-anisyl-1,3,5-trithianes 73a and b were prepared and reacted separately with DMAD; in each case, the two forms yielded the same m-dithiin.



a. Ar = p-Me.C_6H_4

b. Ar = p-MeO.C_6H_4

Attempts to establish the configuration of the m-dithiins prepared using the above procedures by means of standard spectroscopic methods (i.e. ^{1}Hnmr with NOE* studies[79,80], and ^{13}Cnmr[75-78]) were unsuccessful, and so an X-ray study was carried out on a crystal of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a). The computer drawn diagram (overleaf) gives an idea of the spatial arrangement of atoms in a molecule of the sample. The ring has adopted a slightly distorted half-chair conformation in which the sulphur atom at position 3 lies below the face of the molecule. The hydrogen atoms at C-2 and C-4 are trans with respect to each other, and the

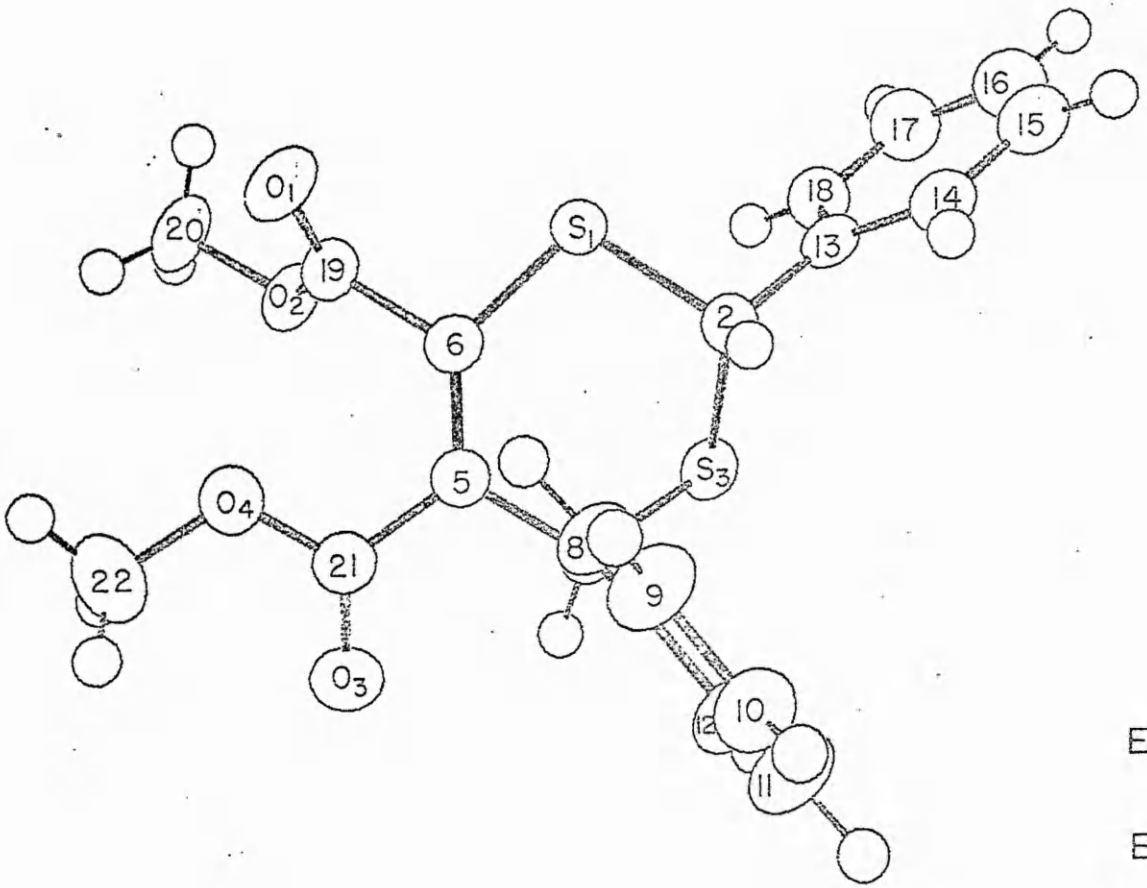


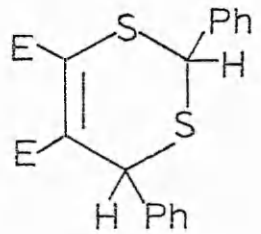
(70a)

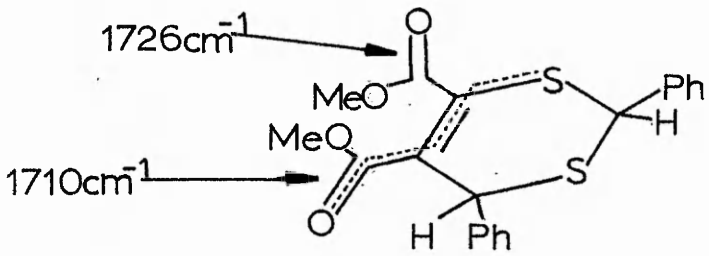
phenyl group at C-2 is equatorial. The ester carbonyl group at C-5 was shown to be in the plane of the double bond, while that at C-6 was distorted out of the plane. This enables the ir carbonyl absorptions at 1726 and 1710 cm^{-1} to be attributed to the esters on C-6 and C-5 respectively.

* NOE = Nuclear Overhauser Enhancement

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)





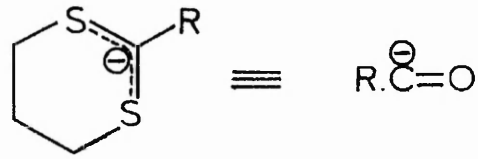


(70a)

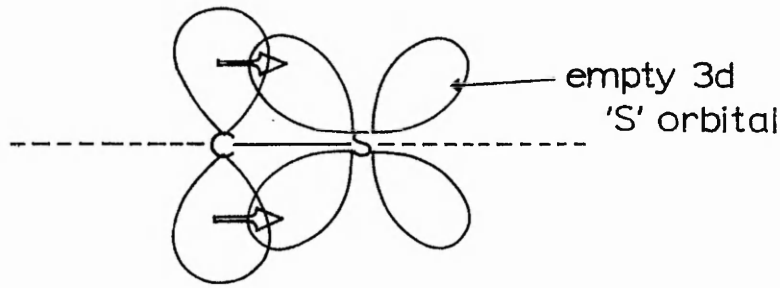
2. Reactions of m-dithiins

A. Proton Abstraction and Subsequent Alkylation

The great attribute of m-dithianes is their propensity to undergo clean proton abstraction at C-2 when treated with strong bases such as n-butyllithium; they are thus masked acyl carbanion equivalents[25].



The reason for this ease of proton abstraction or relatively high acidity at C-2 is the unique carbanion stabilisation afforded by the neighbouring sulphur atoms. It is widely believed[81-83] that the reason for the stability of α thiocarbanions relative to their oxo-analogues is the presence of $d\pi$ -$p\pi$ back-bonding of the carbanion lone pair into the vacant 3d orbital on the adjacent sulphur atom.



This would account, for example, for the variation in pKa values for the compounds shown below[84].

	$PhCH_3$	$(PhS)_2CH_2$	$(PhS)_3CH$
pKa	48	30.8	22.5

It does not, however, account for the fact that the C-S bond in $HSCH_2^{\ominus}$ is longer than that in $HSCH_3$[85] contrary to the expected shortening which should occur if $p\pi$ -$d\pi$

bonding (and hence some degree of double bond character) is present.

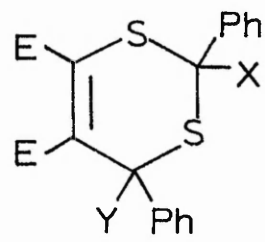
In spite of the continuing arguments concerning the nature of the stabilisation of α thiocarbanions, it is undeniable that their utilisation has been an invaluable tool for the organic chemist in recent years.

By analogy with m-dithianes, it might be expected that m-dithiins such as dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) would also form C-2 carbanions when treated with strong bases. Reaction with appropriate electrophiles should then lead to many interesting and varied products.

Accordingly, a solution of m-dithiin 70a was treated at -78° with one equivalent of n-butyllithium and the dark solution which formed was quenched with deuterium oxide. Nmr analysis of the material so produced indicated that specific monodeuteration had taken place, as evidenced by the disappearance of the methine proton absorption at δ 4.78 ppm. Furthermore, the ester methyl absorptions at δ 3.86 and 3.64 ppm had moved upfield by 0.1 and 0.3 ppm respectively. This shift was unexpected, since replacement of one of the methine protons by deuterium would hardly be likely to have much effect on the magnetic environment of the ester methyl protons.

Reaction of the anion with methyl iodide in a similar experiment gave an excellent yield of another new compound whose nmr characteristics were consistent with the product of a reaction of the same type as that just described. At this point it was not known whether the proton abstraction had taken place at C-2 or at C-4.

(74)
a. X=D, Y=H
b. X=H, Y=D

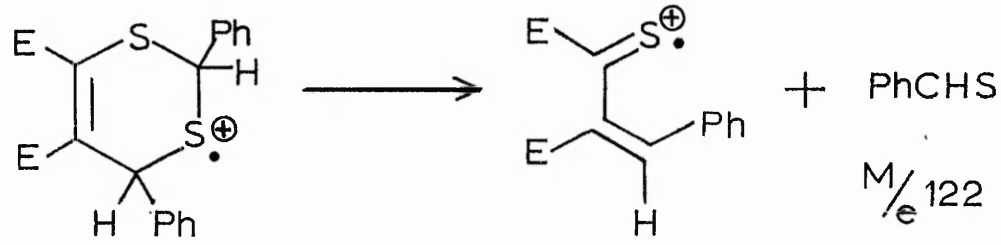


(75)
a. X = Me, Y=H
b. X = H, Y = Me

E = CO_2Me

Three methods were employed to resolve this problem, namely, analysis of mass spectral fragmentation patterns, ozonolysis and dethioacetalisation.

The mass spectral fragmentation of m-dithiins has been shown[86] to commence with the loss of thiobenzaldehyde as shown below (see also page 26).



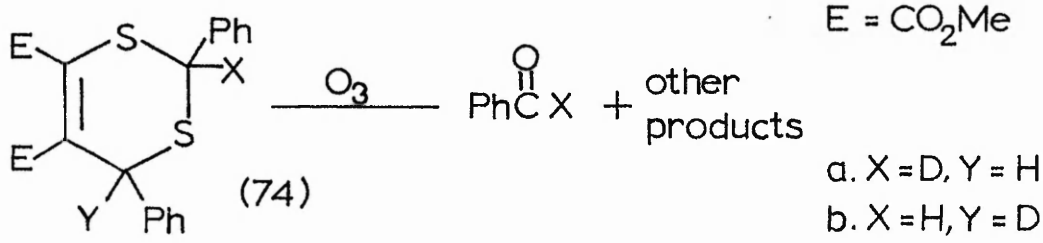
M/e 386

M/e 264
(metastable peak)

The spectra from the deuterated and methylated m-dithiins, 74 and 75, both gave initial fragmentation which indicated the loss of thiobenzaldehyde ($^{M}/e122$), and not deuterothiobenzaldehyde ($^{M}/e$ 123) or thioacetophenone

(^{M}/e 136) respectively.

Secondly, ozonolysis of m-dithiins such as 70a has been shown [71] to result in the formation of benzaldehyde, (isolated as its 2,4-dinitrophenylhydrazone). When this procedure was applied to the deutero-derivative, 74 (as well as to the unchanged m-dithiin 70a as a control), a complex mixture resulted from which benzaldehyde was isolated, again as the 2,4-dinitrophenylhydrazone. The derivative was characterised both by melting point and by mass spectrometry; no deuterated hydrazone was observed in the mass spectrum.



(74)

Final proof was provided by the specific dethioacetalisation of the methyl-substituted m-dithiin, carried out using the procedure of Seebach [25] which involves the reaction of a dithioacetal (or dithioketal) with mercuric oxide and mercuric chloride. The methyl compound was found to yield benzaldehyde (isolated as the 2,4-dinitrophenylhydrazone) and not acetophenone, which would have been expected, had methylation occurred at C-2. (Again a control experiment was carried out on the unsubstituted m-dithiin.)

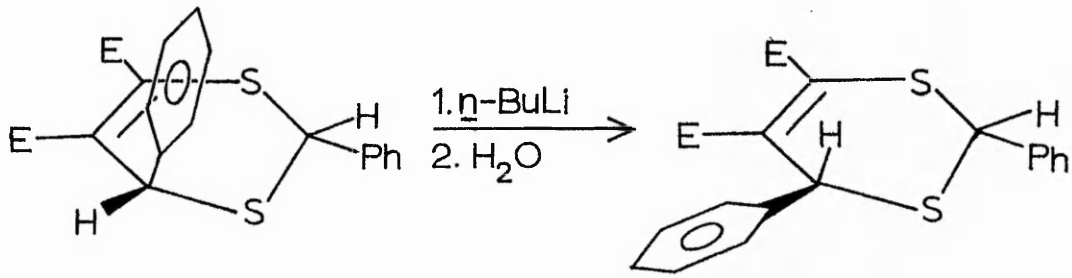
On the basis of the three pieces of evidence presented, it is clear that anion formation does not involve C-2. It would seem reasonable to assume, therefore,

that the reactions had taken place at C-4. The nmr shifts mentioned on page 40 for the deutero compound were worrying however, so as a check, the lithiation was repeated, but the anion quenched with water rather than deuterium oxide.

The nmr spectrum of the product again showed the slight upfield shift in the ester methyl protons. It also revealed a downfield shift in the replaced proton; this had moved from δ4.80 to 4.96 ppm. In fact the product was completely different from the starting material both in its melting point and in its uv and ir absorption characteristics. The changes in the spectra were very revealing. The ir carbonyl absorptions had shifted from 1726 and 1710 cm^{-1} to 1735 and 1715 cm^{-1}, and the uv maximum at 289 nm was reduced in intensity; both these observations indicate that conjugation was diminished in the product.

Initially, it was thought that these changes could be explained by the theory that reprotonation had taken place on the opposite side of the ring to give the C-4 epimer of the starting material.

i.e.

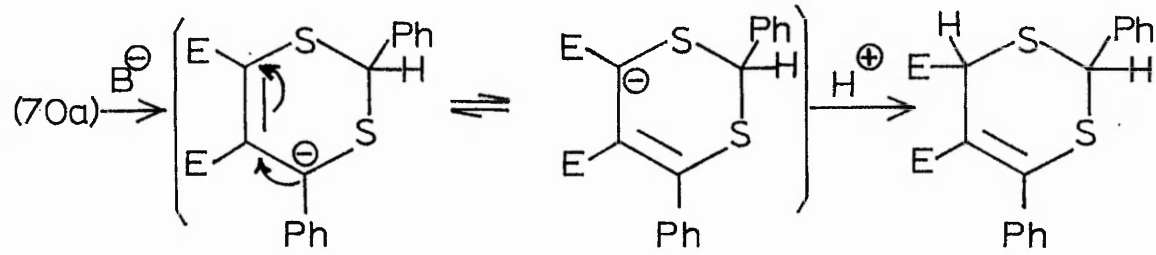


E = CO_2Me

However, close examination of the off-resonance proton decoupled ^{13}C nmr spectrum from the new isomer revealed that one of the benzylic carbon atom signals had changed from

a doublet to a singlet, indicating that the carbon had lost the proton which had been bonded to it. (Carbon atoms attached to 'n' protons appears as 'n + 1' peaks when the sample compound is subjected to off-resonance proton decoupling.) Moreover, one of the signals from an ester-bearing carbon atom appeared as a doublet (n + 1 peaks; n = 1) showing that this carbon atom had gained a proton. The conclusion to be drawn from these results is that tautomerism had taken place, involving a proton shift from C-4 to C-6.

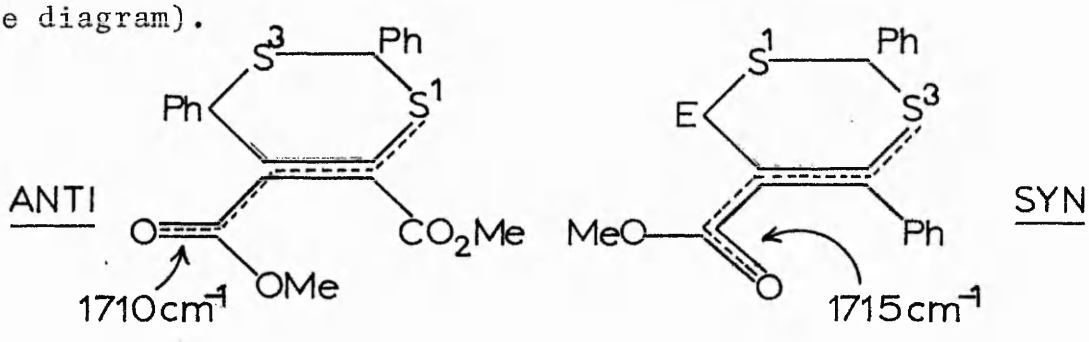
E = CO_2Me
B = base



(76a)

Final confirmation of the structure of the product as dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a) was obtained by X-ray crystallography. The computer drawn X-ray structure for the 6H-tautomer, 76a, is indistinguisable in conformation from that of the 4H-compound, 70a, the C-2 phenyl group being equatorial and the ring protons lying trans with respect to each other. The ester carbonyl function at C-5, which was previously conjugated through the double bond to S-1, is now conjugated through the repositioned double bond to S-3. Although the increase in this carbonyl frequency on formation of the 6H-tautomer was only slight (from 1710 to 1715 cm^{-1}), this can nevertheless be attributed

to the fact that the carbonyl at C-5 is now syn with respect to the other vinyl substituent (Ph) whereas in the 4H-tautomer, 70a, it had been anti with respect to the vinyl substituent (CO_2Me) and conjugation therefore more efficient (see diagram).

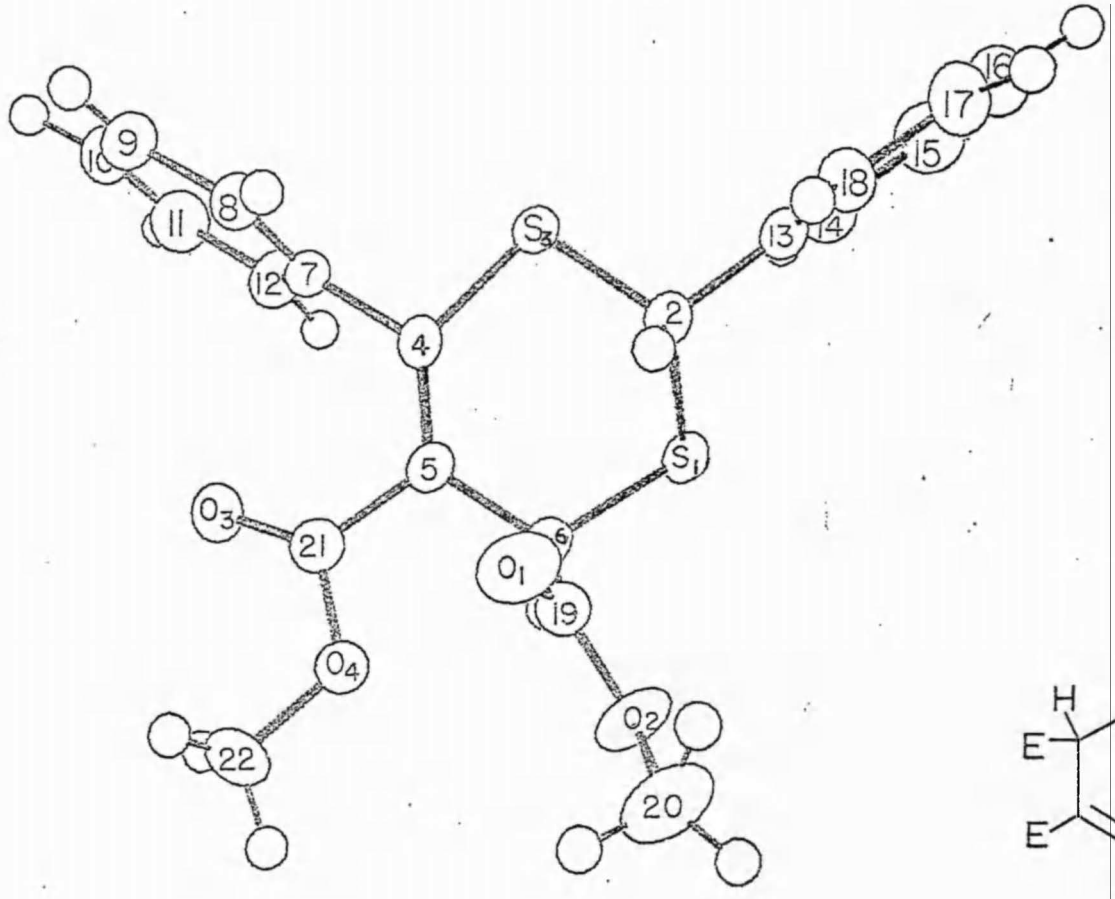


4H-tautomer (70a) 6H-tautomer (76a)

Despite spectroscopic indications to the contrary, it must be assumed that the 6H-tautomer, 76a, is the more thermodynamically stable isomer. When treated independently with n-butyllithium followed by water, this isomer was completely unchanged. A full comparison of the spectroscopic data from the 4H-and 6H-tautomers 70a and 76a is given below in Table 1.

Acylation of the anion (which was formed by treatment of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) with one equivalent of n-butyllithium) with acetic anhydride gave dimethyl 6-acetyl-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76d)

Dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a)



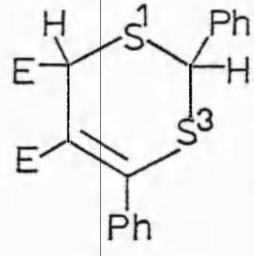
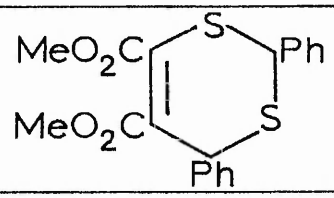
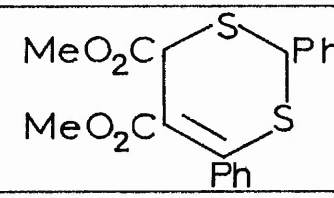
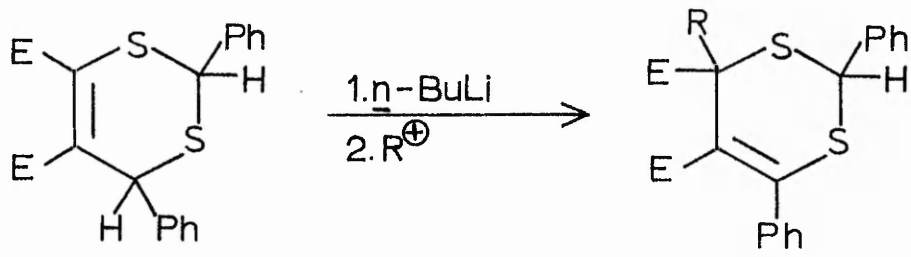


TABLE 1.

	 (70a)	 (76a)
^{1}Hnmr, δ, ppm ($CDCl_3$)	7.32 (s, C_6H_5) 5.40(s,H-2), 4.80(s,H-4) 3.87, 3.65(s,CO_2CH_3)	7.28 (s, C_6H_5) 5.52(s,H-2), 4.96(s,H-6) 3.75, 3.35 (s,CO_2CH_3)
^{13}Cnmr, δ, ppm ($CDCl_3$)	165.6) 164.5) ($\underline{C}O_2Me$ at C6 and C5) 145.6 (C-6) s* 121.2 (C-5) 45.8 (C-4) d* 45.1 (C-2)	170.9 ($\underline{C}O_2Me$ at C-6) 165.8 ($\underline{C}O_2Me$ at C-5) 154.7 (C-4) s* 115.5 (C-5) 47.6 (C-6) d* 44.8 (C-2)
ν max, cm^{-1}	1726 (C=O at C-6) 1710 (C=O at C-5)	1735 (C=O at C-6) 1715 (C=O at C-5)
λ max. cm^{-1} (MeOH)	287 (ε 14,000) 225 (ε 9,800)	289 (ε 14,000) 226 (ε 7,200)

* indicates the multiplicity of the signal in the off resonance proton decoupled spectrum.



(70a) (76)

a. R = H
b. R = D
c. R = Me
d. R = CO.Me

70-90%

E = CO_2Me

Similar ^{1}Hnmr, uv and ir characteristics for the m-dithiins 76 a-d suggest that they are all examples of the 6H-tautomer rather than the 4H-tautomer.

Attempts to acylate with propionyl chloride and benzylate using benzyl bromide were unsuccessful, nmr analysis indicating that none of the desired compounds were present in the reaction products. Allylation with allyl bromide seemed to be promising, the 6-allyl derivative being observed as part of the product mixture by nmr spectroscopy. The substance could not be isolated by chromatography, however, due to the similarity in Rf of the components of the mixture.

Carboxylation was also unsuccessful, no reaction occurring even after the deprotonated m-dithiin had been in contact with carbon dioxide at room temperature for prolonged periods. Since acetylation using acetic anhydride had been successful, the failure of the carboxylation was

a little surprising.

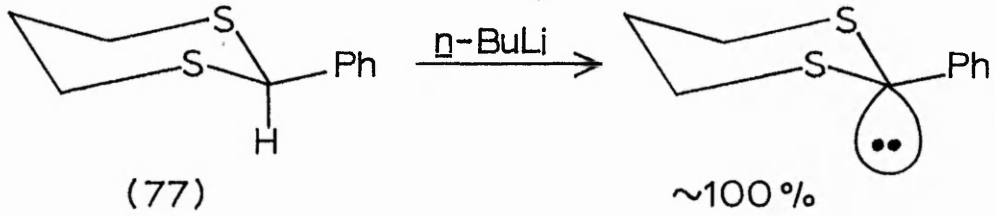
An attempt was made to prepare a β -ethylamine m-dithiin derivative by reacting a solution of the anion with 2-chloroethyldimethylamine. The resultant mixture was too complex to merit separation.

In the light of the knowledge that the C-4 proton in these m-dithiins is the one most readily abstracted by base, attempts were made to remove the less acidic C-2 proton. Since C-2 protons in m-dithianes have been selectively removed using n-butyllithium[24], no particular problems were envisaged in applying this to m-dithiins.

Accordingly, dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was treated with two equivalents of n-butyllithium at -78°C. Deuteration followed by nmr analysis of the residue revealed that a mixture had formed from which no single pure product could be isolated. The 6H-tautomeric 6-methyl compound, 76c, was treated with n-butyllithium at various temperatures below 0°, but surprisingly, clean proton abstraction was never observed; instead, either mixtures or unchanged starting material were obtained.

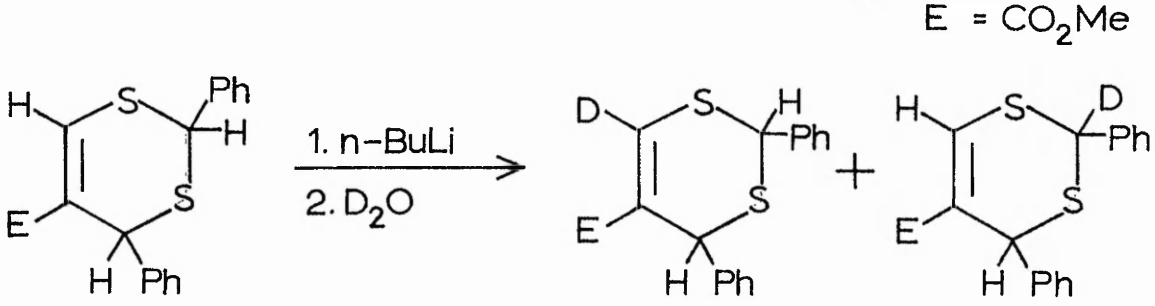
Eliel has shown[87] that the equatorial 2H of m-dithiane has a greater kinetic acidity than the axial 2H. Since the 2H in the m-dithiins under investigation has been shown by X-ray diffraction studies to be axial, this may account in part for the difficulty encountered in attempts to remove it. It must be stressed however, that this effect should be marginal since 2-phenyl-m-dithiane (77, in which the 2H has been shown[88] by X-ray diffraction to be axial)

is readily deprotonated by one equivalent of n-butyllithium below -50° [25].



(77) ~100%

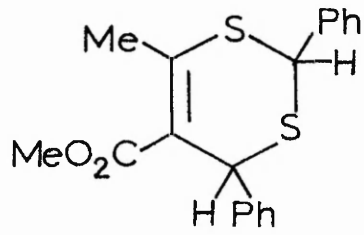
The present work reveals that the replacement of the vinyl proton at C-6 in 4H-tautomeric m-dithiins is also possible in appropriate cases. Treatment of methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b) with n-butyllithium, followed by deuterium oxide, led to a mixture of the C-2 and C-6 deuterated material:-



(70b) (78a) 6 : 4 (nmr) (78b)

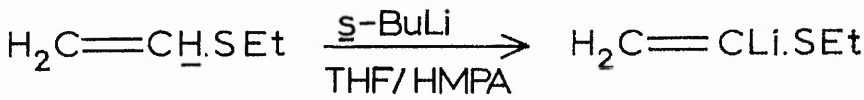
(Notably, this was the only instance where any C-2 substitution was encountered.) No reduction in the intensity of the nmr signal from the 4H was observed.

In a similar experiment, when methyl iodide was used instead of deuterium oxide, the 6-methyl-4H-m-dithiin 78 was isolated.



(78)

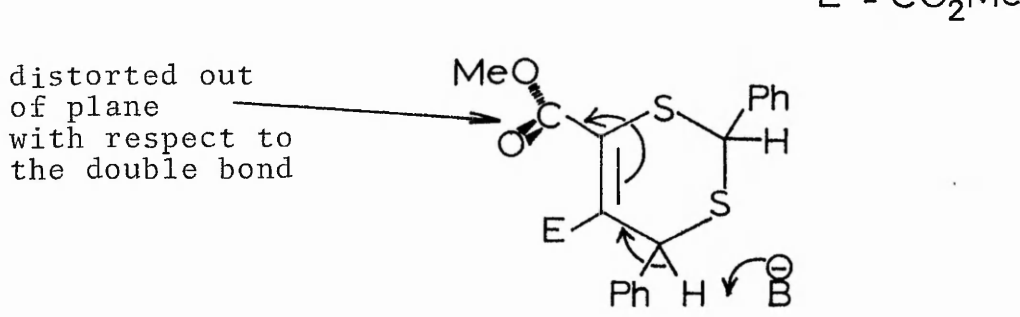
In order to remove vinyl protons which are also adjacent to sulphur atoms, stronger bases than n-butyllithium are normally needed. This is illustrated by the deprotonation of the vinyl thioether, 79, which was carried out[89] using s-butyllithium in tetrahydrofuran-hexamethylphosphoric triamide (HMPA and other highly polar solvents tend to increase the dissociation of alkyllithiums and hence their basicity). It is surprising therefore, that compounds such as the



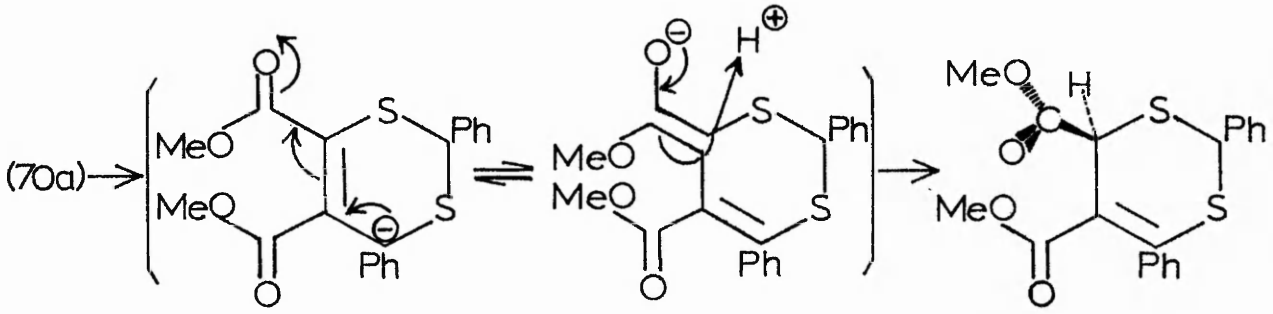
(79)

6-methyl m-dithiin, 78, can be prepared using n-butyllithium.

The absence of a stabilising ester group at C-6 has rendered the proton at C-4 even less susceptible to attack than either of the other protons at C-2 and C-6. In cases where an ester group was present at C-6, as in 70a, the carbonyl function was shown by X-ray diffraction to be distorted out of the plane of the double bond and thus inefficient as regards conjugative stabilisation.



To rationalise these observations, it must be assumed that when proton abstraction occurs at C-4, the carbonyl attached to C-6 becomes aligned with the double bond as shown below, thus affording some conjugative stabilisation to the anion. On quenching, the C-6 carbonyl then reverts to an out of plane conformation to relax the steric hindrance between the adjacent ester methoxy groups; the carbonyl at C-5 then becomes conjugated with S-3 through the double bond as shown by the X-ray study (page 46).



Having established a route to the series of tautomeric m-dithiins, 76a-d, it was decided to study the effect of other bases on m-dithiins.

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was treated with sodium hydride in solvents such as N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and toluene. Typically, a mixture was obtained, which was shown to consist of starting material and only traces of the 6H-m-dithiin tautomer, 76a; clean deuteration or alkylation did not occur.

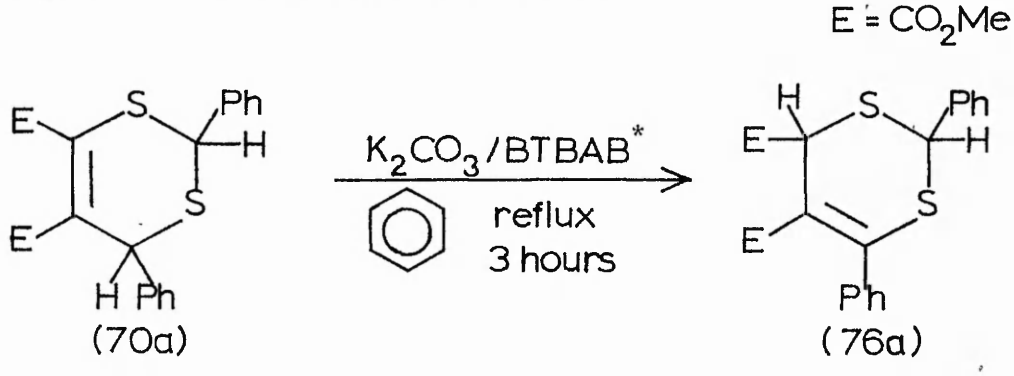
Phase-transfer catalysis has in recent years provided innumerable examples of carbanion formation and subsequent alkylation with increased efficiency[90-93].

Utilisation of this technique has enabled reactions to occur between immiscible aqueous and organic phases. The use of polar aprotic solvents such as DMF, DMSO and THF (which are expensive and require thorough drying in order to prevent solvation of the attacking nucleophile by water) can now be avoided in a large range of reactions, particularly alkylation of carbon acids. Under normal circumstances an aqueous phase containing the nucleophile and an organic phase containing the substrate together with an alkylating agent are used. The catalyst[94] is usually a quaternary ammonium halide carrying bulky substituents or a crown ether, and enjoys solubility in both aqueous and organic phases. Complexation occurs between nucleophile and catalyst, enabling the former to enter the organic phase as a largely unsolvated ion-pair and react with the substrate.

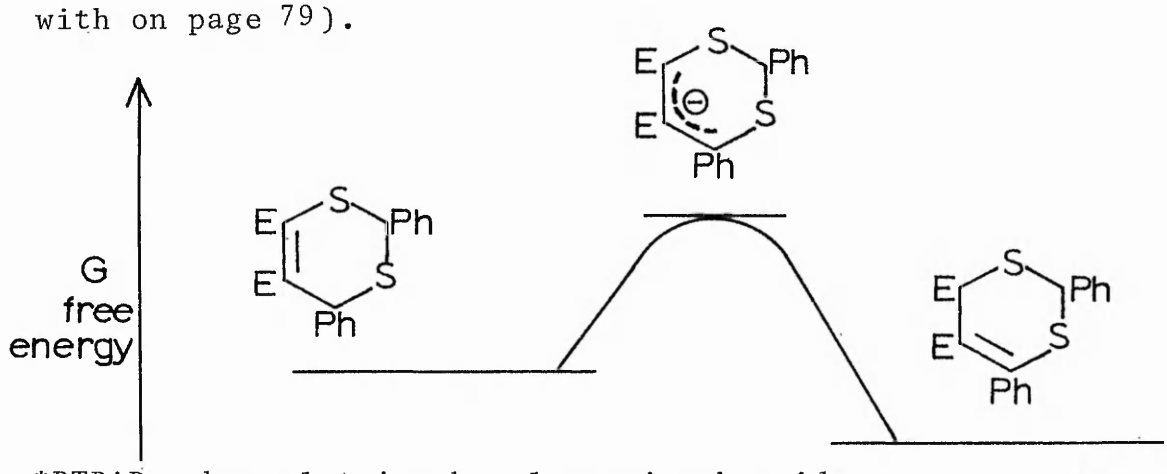
Dry solvents are not required but for particularly water-sensitive substrates, water can be excluded completely and a solid–liquid system can be used. An example of this, is the oxidation of organic substrates using solid potassium permanganate catalysed by crown ethers. Solid potassium or sodium carbonate can also be used as a proton abstractor in alkylation reactions[95], and is normally superior to the more common carbonate-aqueous acetone system. In this case, however, the carbonate ion is not actually transferred into the organic phase; instead the reaction occurs on the surface of the solid and the deprotonated substrate becomes ion-paired with the catalyst in the organic phase prior to alkylation.

Since the m-dithiins are obviously weaker acids

than water, a non-aqueous system is needed for proton abstraction. When the solid potassium carbonate method of Makosza[95] was applied to the 4H-m-dithiin, 70a, it was found that complete tautomerism occurred giving the 6H-tautomer, 76a. Alkylating agents such as methyl iodide, dimethyl sulphate and ethyl iodide were included, but no detectable alkylation occurred. Deuterochloric acid was used to quench the reaction in order to avoid contact with aqueous base, but no reduction in the intensity of the nmr signals from the ring protons was observed.



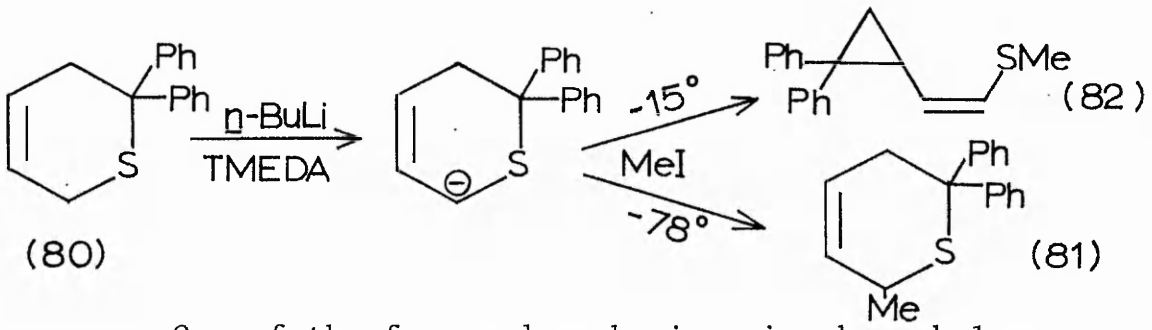
To explain these observations, it must be assumed that the concentration of deprotonated m-dithiin at any given time is extremely low. The tautomerism and reprotonation steps proceed quickly and are essentially irreversible, giving the more thermodynamically stable 6H-tautomer. When the solvent is wet, side reactions occur (these are dealt with on page 79).



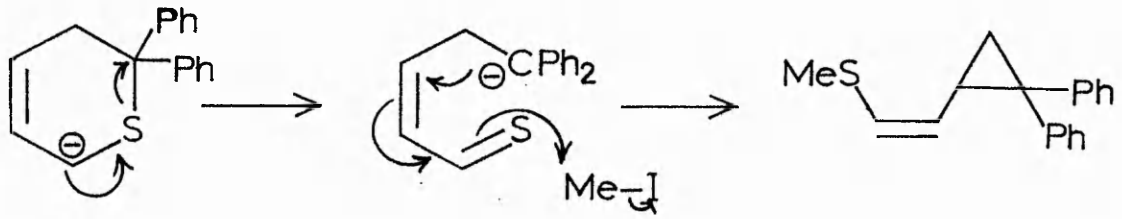
*BTBAB = benzyl tri-n-butylammonium bromide

An interesting rearrangement of a carbanion derived from a cyclic allyl thioether has been reported by Biellmann and Ducep[96]. When 6,6´-diphenylthiacyclohex-3-ene (80) was treated with n-butyllithium in the presence of N,N,N´,N´-, tetramethylethylenediamine (TMEDA) or diazabicyclo [2.2.2] octane (DABCO) at -80° in tetrahydrofuran and methyl iodide was added, alkylation took place forming 2-methyl-6,6´-diphenylthiacyclohex-3-ene (81).

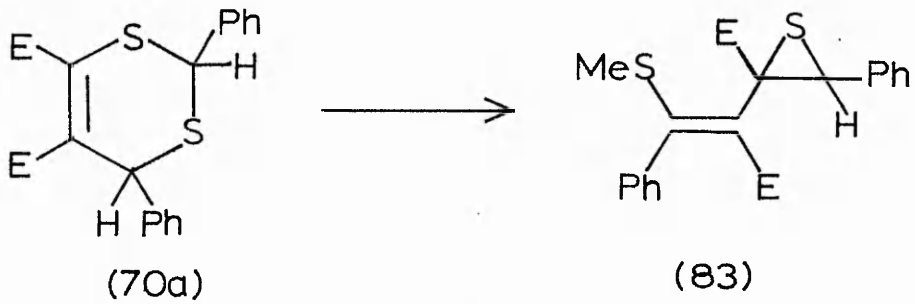
When the reaction was allowed to warm up to -15° prior to alkylation, however, a rearrangement occurred giving the cis-cyclopropane methyl thioether, 82.



One of the favoured mechanisms is shown below.

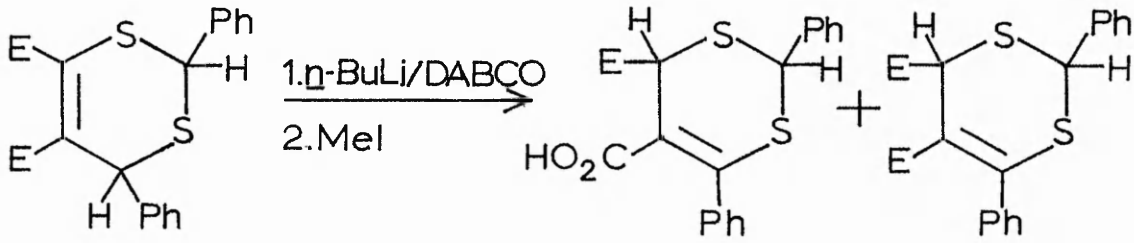


An analogous rearrangement in a m-dithiin such as dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) would lead to the thiiran 83.



The reaction of 70a with n-butyllithium under identical conditions to those used by Biellmann to produce the unusual rearrangement, gave in 32% yield 2,4-diphenyl-6-methoxycarbonyl-6H-m-dithiin-5-carboxylic acid (84). The second product was the corresponding 6H-tautomeric diester, 76a (46%).

E = CO_2Me



(70a) (84) (76a)

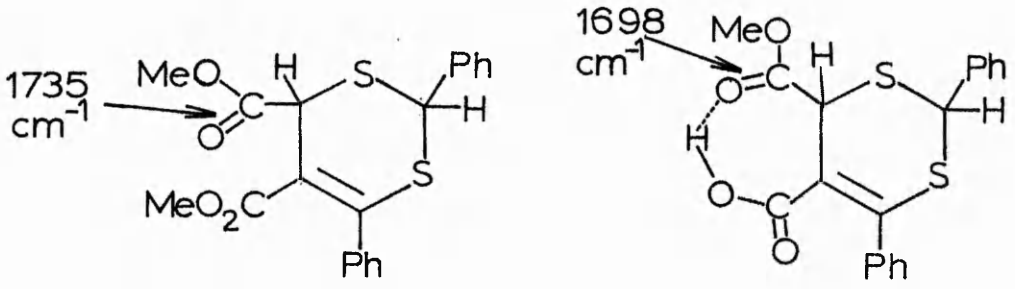
In retrospect, it is not too surprising that the m-dithiin reacted differently than Biellmann's thiacyclohexene, because of the anion stabilising effect of the ester groups.

The yield of the monoacid 84 was increased to 62% when methyl iodide was replaced by water, but the diester 76a predominated when the reaction was quenched with acid.

The assignment of the structure of the monoacid 84 was based on microanalysis, ^{1}Hnmr and ^{13}C nmr data. A comparison of the ^{13}C shifts of the ring carbon atoms with those of 4H-and 6H-m-dithiin tautomers clearly showed that 84 was a member of the latter class. The acid function was shown to be attached to C-5 rather than C-6 by observing the changes produced in the shifts of the olefinic carbon atoms in the ^{13}C spectrum when the carboxylate anion was produced by treatment with triethylamine. These were then correlated with those from model compounds*, showing that the acid function

*This technique is explained fully on page 83, and the data for the model compounds are given in Appendix B.

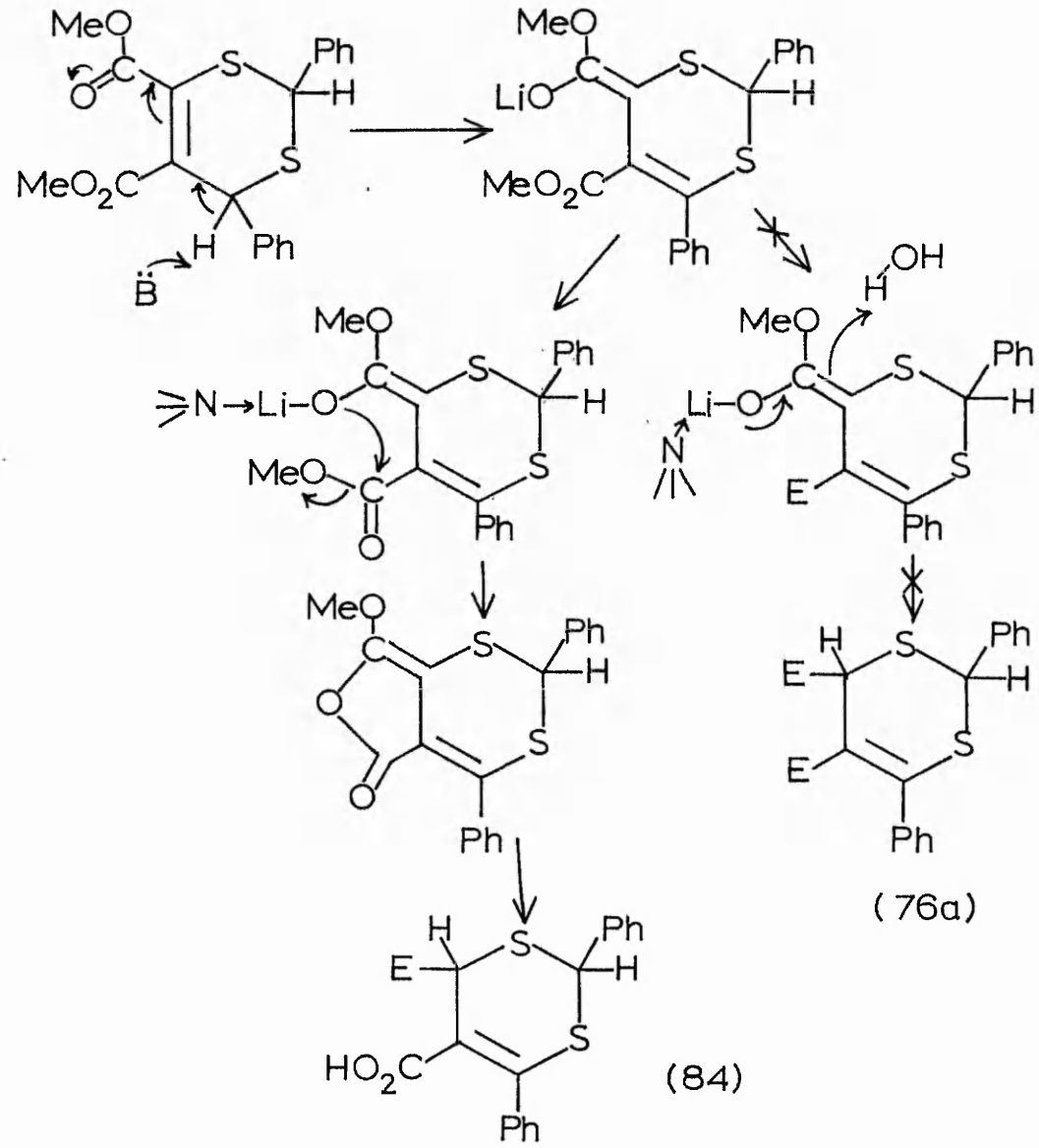
was in conjugation with the double bond. The ir carbonyl frequency (1698 cm^{-1}) for the ester in 84 is slightly anomalous, in that it compares with a value of 1735 cm^{-1} for the ester at C-6 in the 6H-tautomeric diester, 76a. This reduction in frequency of 37 wavenumbers for the ester may have been caused by hydrogen bonding with the adjacent acid as shown, but this seems doubtful.



(76a) (84)

In spite of this, the bulk of the evidence supports the assignment of 84 as the correct structure.

With regard to the mechanism of the formation of 84, it was established by control experiments with DABCO (or TMEDA) and aqueous base that the tertiary amine is necessary for the reaction to proceed, and the hydrolysis is not simply the result of the formation of lithium hydroxide during quenching. Presumably the role of the tertiary amine is to complex with the lithiated m-dithiin, thereby separating the ion-pair and increasing the basicity[97] of the anion. That this increase should be manifest in an attack on a neighbouring ester function in preference to proton abstraction from water is surprising.

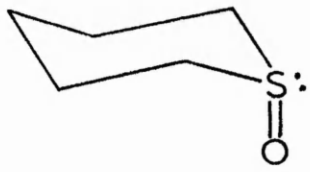


Reaction of the acid 84 with diazomethane at 0° gave the 6H-tautomeric diester 76a in quantitative yield.

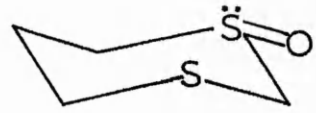
Two attempts were made to decarboxylate the acid, 84. In the first of these, it was heated with powdered glass, and in the second, with cuprous oxide in boiling pyridine. Neither method was successful, an intractable mixture being obtained in each case.

B. Oxidation

m-Dithiins such as dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) can be expected to undergo oxidation primarily at the most electron rich sulphur atom, which is S-3. Other sulphur-containing hetrocycles such as thiopyrans[98] and m-dithianes are known to undergo oxidation at sulphur readily, the reaction normally resulting in isomeric mixtures of axial and equatorial sulfoxides. For thiopyran sulphoxide (85), the axial conformation is preferred[99], whereas the m-dithiane monosulphoxide (86) exists almost totally in the equatorial form[100].



(85)



(86)

The ratio of axial and equatorial sulphoxide isomers produced from substituted sulphur heterocycles frequently varies according to the nature of the oxidising agent employed [98,101]. Although general trends have been observed in the preference for a particular isomer when a given oxidising agent is used (e.g. dinitrogen tetroxide has been shown to lead to the formation of the more thermodynamically stable form[98]) no reliable predictions can be made.

The m-dithiin, 70a, was treated with several oxidising agents and the results are summarized in Table 2.

TABLE 2.

Oxidant	Solvent	Temp. °C	Product	Yield %	Ref.
MCPBA	CH_2Cl_2	0	S-3 Sulphoxide	58	98
MCPBA/$NaHPO_4$	CH_2Cl_2	22	S-3 Sulphoxide	35	110
HIO_4	CH_3CN or $(C_2H_5)_2O$	reflux	-	-	109
$NaIO_4$	*	reflux	-	-	111
$NaIO_4$	aq.CH_3CO_2H	50	S-3 Sulphoxide ≠	29	111
KIO_4/BTEAC	H_2O/CH_2Cl_2	22	-	-	
$Bu_4N^{\oplus}IO_4^{\ominus}$	CH_2Cl_2	40	-	-	112
$KMnO_4$	$(CH_3)_2CO$	0	- ≠	-	113
$KMnO_4$/18cr 6	CH_2Cl_2	22	-	-	114
$NaClO_2$/HCl	aq.pyridine	45-80	mixture	-	115
CrO_3-pyridine complex	CH_2Cl_2	22	mixture ≠	-	116
PhIO	toluene	110	-	-	117
H_2O_2	$CH_3CO_2CH_2CH_3$	22	S-3 Sulphoxide ≠	51	118
$H_2O_2/(NH_4)_2MoO_4$	CH_3OH/CH_2Cl_2	40	S-3 Sulphoxide ≠	62	119

* aqueous acetone, acetonitrile, methanol and tetrahydrofuran were all tried

≠ an excess of oxidant was used

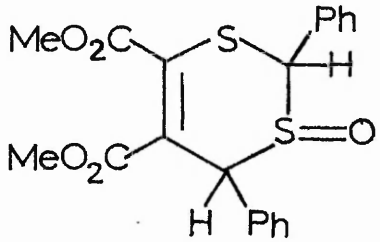
BTEAC = benzyl triethylammonium chloride (Makozsa's catalyst)

MCPBA = m-chloroperbenzoic acid

(The investigation was not exhaustive, and several alternative methods of oxidation were not used. These include distannoxane[102], hydrogen peroxide-selenium dioxide[103], thallium (III) nitrate[104], sulphuryl chloride-wet silica gel[105], iodobenzene dichloride[106], alumina supported periodate[107] and polymer supported peracid[108].)

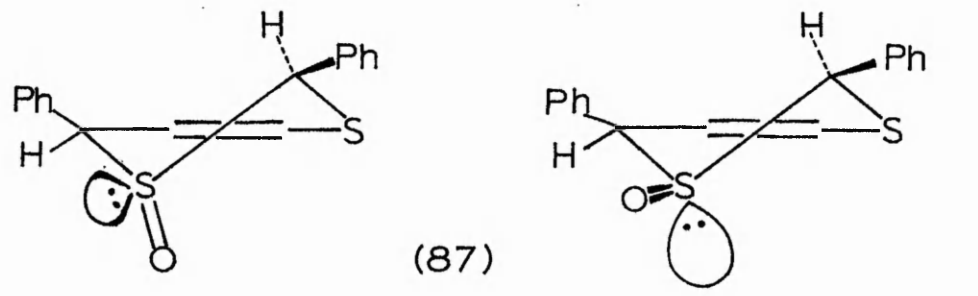
The table shows that many of the reagents used gave either no reaction, or produced a mixture which contained starting material, but from which no product could be isolated. This was not due entirely to lack of sulphide reactivity; rather, it could be attributed in many cases to poor solubility of the substrate in the reaction solvent. The lack of reactivity towards a standard reagent such as sodium periodate[109] illustrates the point.

As expected, the isolated sulphoxide, 87, was shown (nmr) to consist in each case of a mixture of axial and equatorial isomers. No appreciable variation in the ratio (3:1) with the reagent employed was observed, and separation of the isomers was accomplished by dry column chromatography. (The minor isomer had the greater Rf value when dichloromethane was the eluant.)



(87a and b)

In order to evaluate the evidence which has some bearing on the assignment of the isomeric sulphoxides, it is pertinent to illustrate them in the same ring conformation as the m-dithiin, 70a.



a. oxygen AXIAL b. oxygen EQUATORIAL

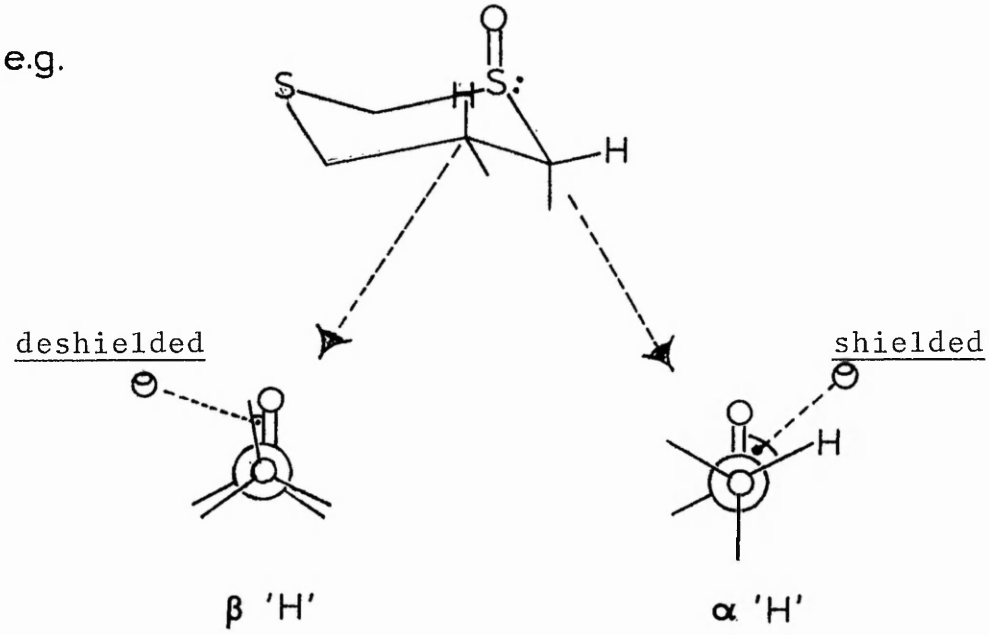
Several criteria are commonly used in the assignment of configuration to isomeric sulphoxides:

A. Proton nmr spectroscopy

The first indications frequently come from a comparison of the proton magnetic resonance spectra from the isomers with that of the parent sulphide. The predictions of the shielding and deshielding effects of a sulphoxide group on neighbouring protons are rather inexact compared with those made for carbonyl functions. This is undoubtedly due to the fact that sulphoxides are non-planar functions and possess a lone pair of valence electrons on the sulphur atom. As a consequence of this dissymmetry, it is virtually impossible to determine accurately the areas of high and low electron density, and hence, shielding and deshielding. It remains therefore, to examine examples

from the literature and to look for pointers as to the effect of the sulphoxide group on the nmr shifts of neighbouring protons.

The main observation[120-122] has been that protons which have a syn diaxial relationship to the sulphoxide group (whether they are attached to α or to β carbon atoms) are deshielded[123,124]. This effect appears to vary (approximately) with Θ, the dihedral angle between the C-H bond and the adjacent sulphoxide, and may be as much as 0.8 ppm for Θ values approaching 0°.



In summary, protons close to the lone pair of a sulphoxide are shielded, and those having a syn axial (or similar) relationship to the sulfoxide are deshielded due to the proximity effect[120].

Applying these guidelines to the m-dithiin sulphoxides 87a and b (page 62) it is clear from Dreiding models that the following effects would be expected in relation to the parent compound 70a:

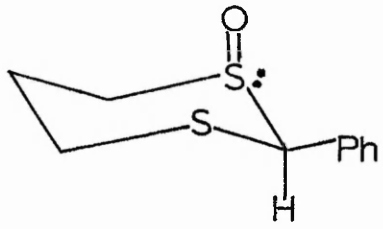
For 87a (H-2 should undergo little change ($\Theta = \sim 170^{o}$)
(H-4 should be slightly deshielded ($\Theta = \sim 30^{o}$)

For 87b (H-2 should be deshielded ($\Theta = \sim 50^{o}$)
(H-4 should be significantly shielded (close proximity of lone pair to proton)

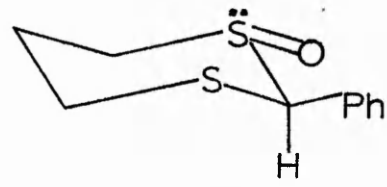
The actual proton shifts observed for the two isomers (in ppm) were -0.18 (H-4), +0.05 (H-2) for 87a, and -0.37(H-4), +0.25(H-2) for 87b. It follows then, that 87a has the axial, and 87b (the major isomer) has the equatorial sulphoxide oxygen.

B. ^{13}C nmr spectroscopy

The ^{13}C nmr shifts of the C-2, C-4 and C-5 atoms in cis- and trans-m-dithiane-1-oxides (relative to m-dithiane) allow an accurate assignment of the configuration of the sulphoxide to be made[125]. Consequently, these shifts for cis-and trans-2-phenyl-m-dithiane-1-oxides (88 and 89) were compared with the equivalent shifts in the two isomeric m-dithiin sulphoxides 87a and b. The results are given in Table 3.



(88)
cis



(89)
trans

TABLE 3

Compound	No.	ppm (shift relative to parent sulphide)		
		C-2	C-4	C-5
m-dithiane-3-oxide (trans)	89	+17.9	+22.5	+6.0
" " (cis)	88	+12.6	+14.9	-11.8
m-dithiin-3-oxide (major)	87b	+10.5	+18.0	-4.2
" " (minor)	87a	+12.4	+14.2	+0.1

As expected, the C-2 and C-4 carbon atoms are both deshielded in each case (α-effect)[125]. The correlation, however, with the equivalent carbon atoms in the m-dithiane-1-oxides was not as close as had been hoped. The minor isomeric m-dithiin-3-oxide, 87a, has almost identical C-2 and C-4 shifts to those in the m-dithiane-1-oxide 88 (axial oxygen), but the same shifts for the major isomer, 87b, are significantly different to those for the m-dithiane-1-oxide 89 (equatorial oxygen). The C-5 shifts for the m-dithiin sulphoxides are completely at variance with those for the m-dithiane sulphoxides, but this is hardly surprising since the C-5 atoms have a completely different environment in these substances.

Therefore, the ^{13}C nmr studies tend to support the assignments made from the ^{1}Hnmr spectra, but the value of comparisons with literature data is limited by the lack of truly comparable model compounds.

C. Solvent-induced proton nmr shifts

Aromatic solvent-induced shifts have often been used[101,126,127] to provide evidence for sulphoxide assignments. It has been experimentally established that aromatic systems like benzene are capable of co-ordinating at electron deficient sites (such as the sulphur atom of sulphoxides) within a solute molecule[128]. The result is a shielding effect (of the order of 0.3-0.5 ppm) on neighbouring protons, and it has been proposed[129] that the sulphoxide group is located along the sixfold axis of the benzene molecule.

Accordingly, ^{1}Hnmr spectra for the two isomeric m-dithiin sulphoxides, 87a and b, were recorded in deutero-benzene and the shifts for the methine protons were compared with those recorded in deutero-chloroform. Surprisingly, it was found that the differences were very small indeed. The largest effect was the shielding (by 0.15 ppm) of the C-2 proton in the minor isomer, 87a; molecular models suggest that this is consistent with an equatorial sulphoxide oxygen. Further, the lack of any shielding effect in the spectrum of the major isomer, 87b, (the C-4 proton should be significantly shielded in this instance) together with the fact that the above result is counter to that deduced in the preceding sections, indicates that this technique is unreliable in the present case.

D. Variation in polarity

The configuration of a sulphoxide group can have a

marked effect on the polarity of the molecule as a whole. This is reflected in the fact that sulphoxide isomers can frequently be separated by simple chromatographic techniques. It has been observed for a series of p-substituted thiane-1-oxides that the axial sulphoxide is always eluted prior to its equatorial isomer[98], and in the absence of 'complicating effects', the same is true[101] for the isomer with the more sterically hindered sulphoxide oxygen.

Since in the present work it was found that the minor m-dithiin sulphoxide isomer 87a was eluted first, it can be deduced that this has the axial configuration (in agreement with the conclusions arrived at in Sections A. and B.). Obviously, this evidence is not conclusive, but it is a useful further indication.

E. Infrared spectroscopy

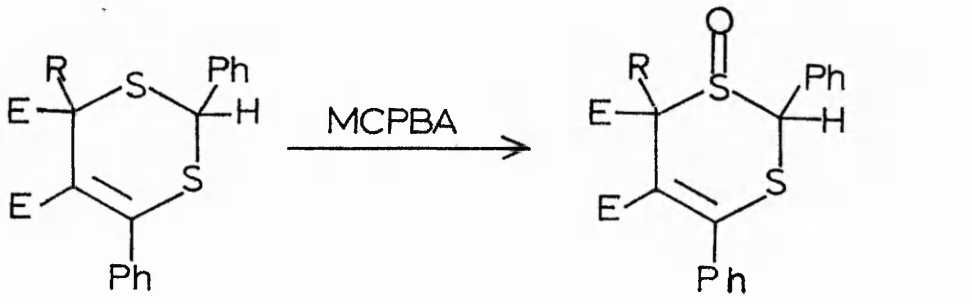
For certain p-substituted thiane-1-oxides[98], the differences in the ir spectra (1,000-1,100 cm^{-1} region) from sulphoxide isomers were diagnostic of configuration. An examination of the ir spectra from m-dithiin sulphoxide isomers 87a and b, however, revealed that the region in question was not comparable with that in the model compounds. In fact there were no significant differences in the ir (or uv) spectra obtained for these isomers.

Summary

The reaction of m-dithiins such as dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) with a suitable

oxidising agent such as MCPBA affords a mixture of two isomeric m-dithiin-3-oxides; the predominating isomer is that in which the sulphoxide oxygen occupies an equatorial position (87b).

When dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a) and its C-6 deutero-derivative (76b) were treated separately with MCPBA at room temperature, the sulphoxides 90a and b were formed in good yield.

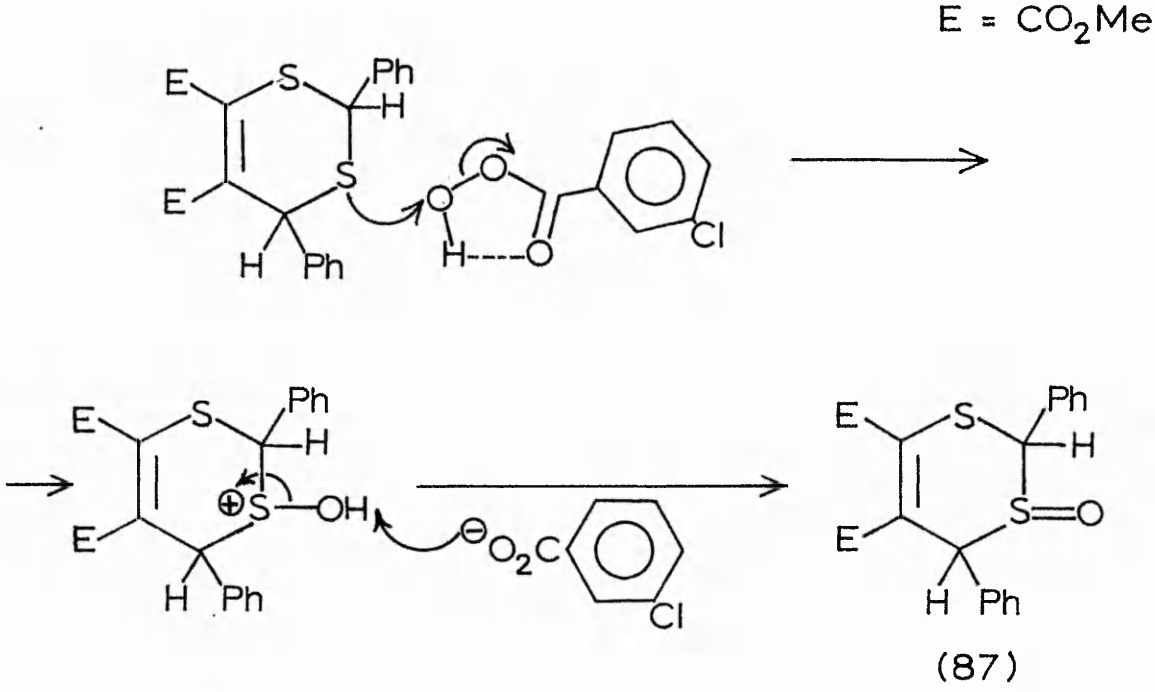


(76) (90)

a. R = H
b. R = D

E = CO_2Me

Sulphoxide formation using peracids such as MCPBA presumably proceeds according to the following mechanism[130].



(87)

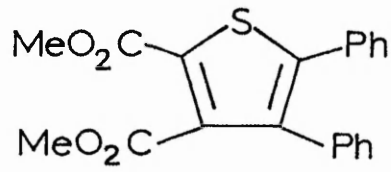
Surprisingly, further oxidation of m-dithiins such as 70a to disulphoxides, sulphones, disulphones or mixed sulphoxide-sulphones was not observed. When m-dithiin monosulphoxide 87b was treated with MCPBA, a mixture was obtained which contained benzaldehyde*, but no products of further oxidation. When an excess of hydrogen peroxide was used at room temperature, no reaction took place; in refluxing ethyl acetate, however, a mixture was formed which contained no new components having greater polarity than the starting material. Reagents such as potassium permanganate in acetone[131] and hydrogen

*see page 71 for an explanation of the formation of PhCHO under acid conditions.

peroxide-ammonium molybdate[119] are reported to oxidise sulphides to sulphones, but Table 2 (page 60) shows that no such reaction took place in the case of m-dithiin, 70a. The reason for the reluctance to undergo further oxidation is unclear.

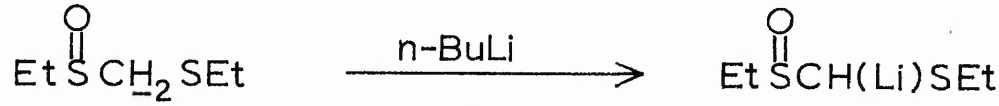
Several other reactions of the m-dithiin-3-oxide, 87b, were investigated:

Pyrolysis of 87b at five degrees above its melting point resulted in complete decomposition to a complex mixture which was shown to contain some dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91).



(91)

In view of the fact that compounds such as the sulphoxide, 92, can be deprotonated easily[132], the sulphoxide 87b was treated with n-butyllithium at -78°;

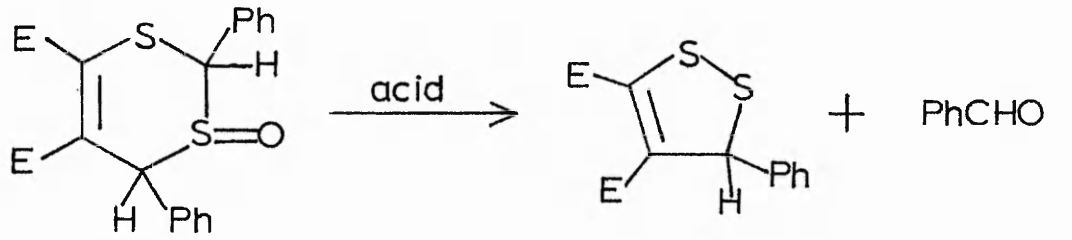


(92)

again, a mixture resulted, from which the thiophen, 91, was isolated. These reactions illustrate the ease with which the molecule undergoes ring contraction (with the loss of sulphur monoxide) to form a stable thiophen.

The acid-catalysed ring contraction of thioacetal monosulphoxides has been used[31,32,59] as a method of

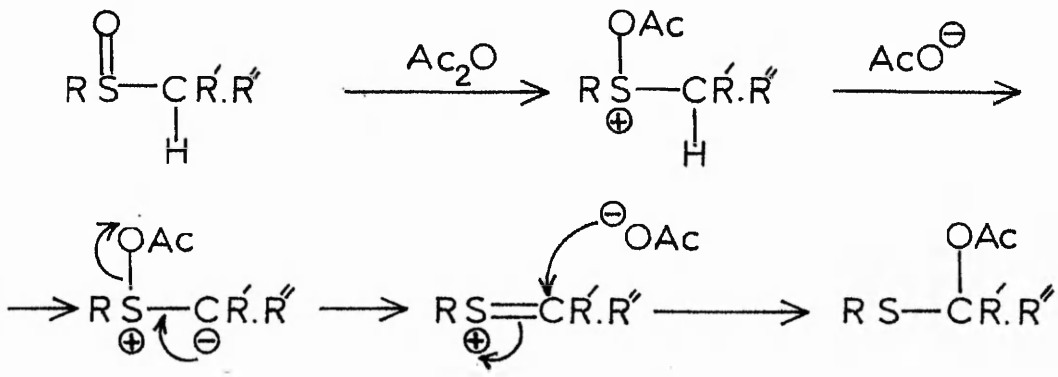
dethioacetalisation for the deprotection of masked acyl carbanion equivalents. Acids such as boron trifluoride, boron trichloride, sulphuric acid, hydrochloric acid and perchloric acid have been reported to effect this transformation, and the course of the reaction for the m-dithiin sulphoxide 87b would be expected to be:



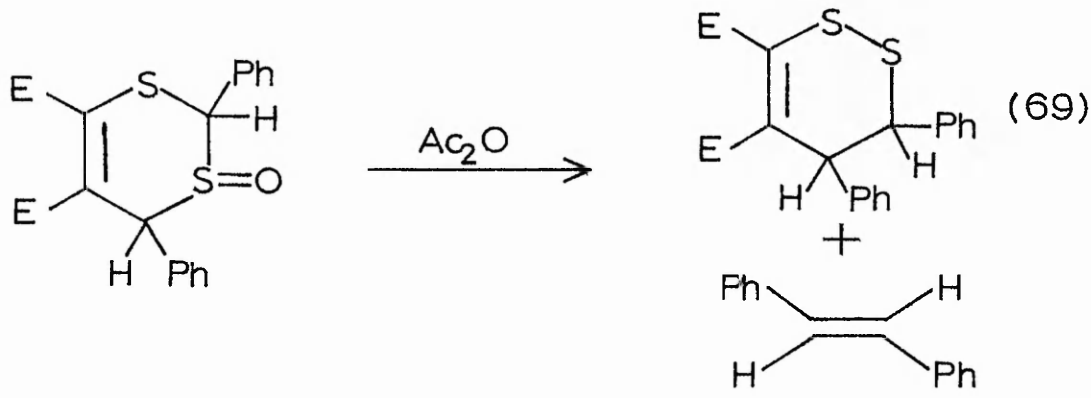
(87) (93) $E = CO_2Me$

The sulphoxide 87b was treated with several of the above acids for prolonged periods, and the formation of benzaldehyde was confirmed in certain cases. Frequently, however, no reaction was observed and the dithiole 93 could not be isolated in those cases where benzaldehyde was detected.

Sulphoxide groups which have α protons are liable to undergo the Pummerer rearrangement when treated with acetic anhydride. This reaction involves reduction of the sulphoxide moiety with concomitant oxidation of the α carbon as shown below.



When sulphoxide 87b was heated in acetic anhydride, it was found that at temperatures below 80° no reaction took place, whereas at 100° all the starting material was consumed and a mixture was formed. This was found to contain dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69) (which is known to arise from the thermal rearrangement of m-dithiins, page 112) and stilbene. No acetylated products were observed, indicating that a simple Pummerer rearrangement had not taken place, and the mode of formation of stilbene in the reaction is not clear.



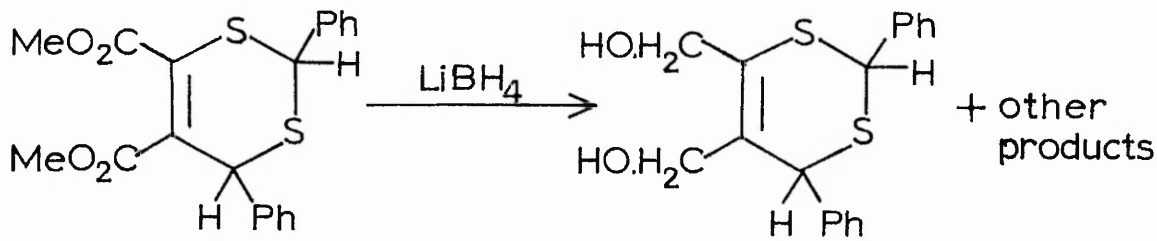
(69)

C. Reduction

Carboxylic esters are notoriously difficult to reduce, usually requiring treatment with lithium aluminium hydride[134] at room temperature or lithium borohydride[135,136] at high temperatures to effect the transition to the alcohol. In certain circumstances, however, esters can be reduced by electrophilic reagents[135,136] such as borane-tetrahydrofuran (THF) or borane-dimethyl sulphide complex.

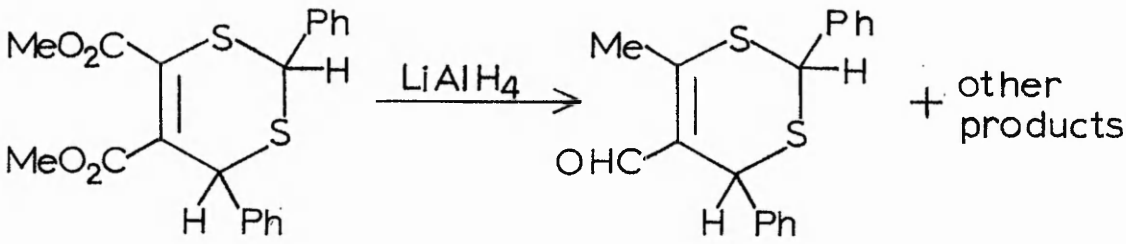
When dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was treated with borane-THF complex, no reaction took place even when a large excess of the reagent in refluxing THF was used. The borane-dimethyl sulphide complex was also ineffective.

Treatment of the same m-dithiin (70a) with two molar equivalents of lithium borohydride in refluxing THF resulted in the disappearance of all the starting material. The product, which was very polar, could not be purified by chromatography. The spectroscopic properties of the crude reaction mixture indicated that hydroxyl groups were present, but could not confirm that the product had the diol structure shown below (94).



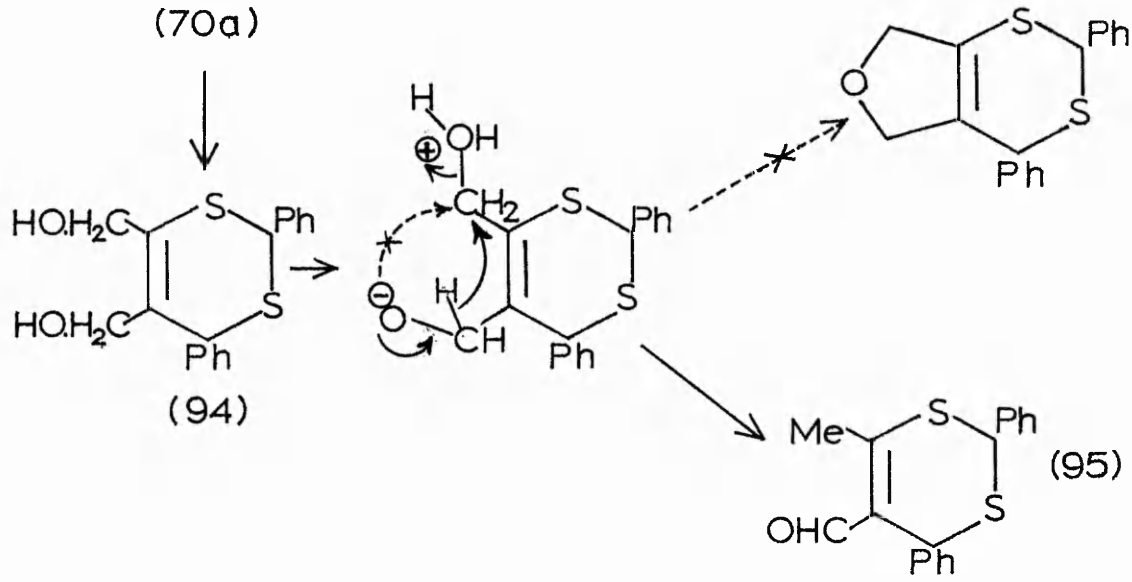
(70a) (94)

Treatment of m-dithiin diester 70a with lithium aluminium hydride at 0^{o} for 30 minutes gave a rather complex mixture which contained no starting material. Purification of the mixture by wet column chromatography led to the isolation of 2,4-diphenyl-6-methyl-m-dithiin-5-carboxaldehyde (95). The structure of the product was assigned on the basis of microanalysis, nmr and mass spectroscopic data. The positions of the C-5 and C-6 substituents may be interchanged, but the very low ir absorption for the aldehyde carbonyl (at $1675cm^{-1}$) indicates that the structure shown (which allows the greatest degree of conjugation) is the most likely one.



(70a) (95)

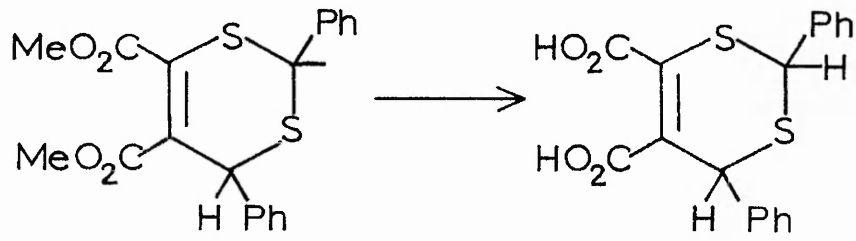
The mechanism by which this unexpected product is formed is unclear, and it seems highly unusual that the adjacent ester functions should react so differently with the reducing agent. One possible mechanism could be as follows:



As this mechanism involves a somewhat dubious hydride transfer step, (in preference to the seemingly more likely ether formation as shown above) it must be accepted with some reservation, despite the fact that other reactions involving a hydride shift are known (e.g. the Canizzaro reaction). However, some evidence for the above mechanism (by use of deuterium labelling) has been obtained for related systems. In these experiments it has been shown[137] that the α hydrogen atom in the alcohol is transferred to the newly formed hydrocarbon.

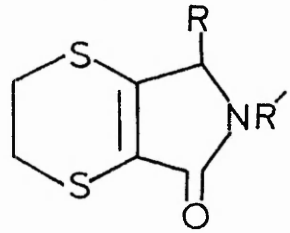
D. Hydrolysis

i. Direct hydrolysis



(70a) (96)

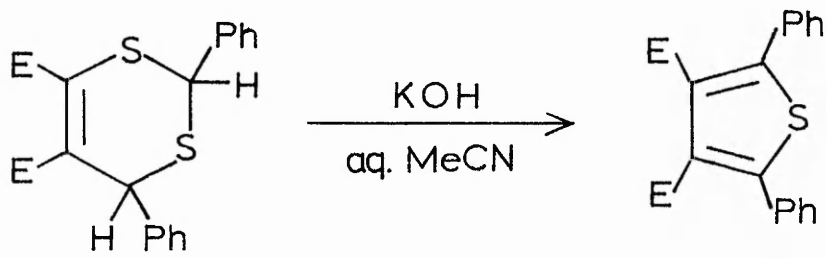
In view of the wide range of biological activity[33-35] possessed by compounds such as the p-dithiin, 14, (see page 8) there is considerable interest in the preparation of the diacid 96 as a precursor to analogous imido-m-dithiin derivatives.



(14)

R, R´= alkyl

The preparation of the required diacid by hydrolysis of 70a presented considerable difficulties. Initially, solutions of potassium hydroxide in aqueous solvents were employed, and one of the main problems was the low solubility of the substrate in these systems. With aqueous THF and aqueous methanol, intractable mixtures were produced; aqueous acetonitrile also gave a mixture of products, but in this case it was possible to isolate a crystalline material from the mixture. This proved to be dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97).

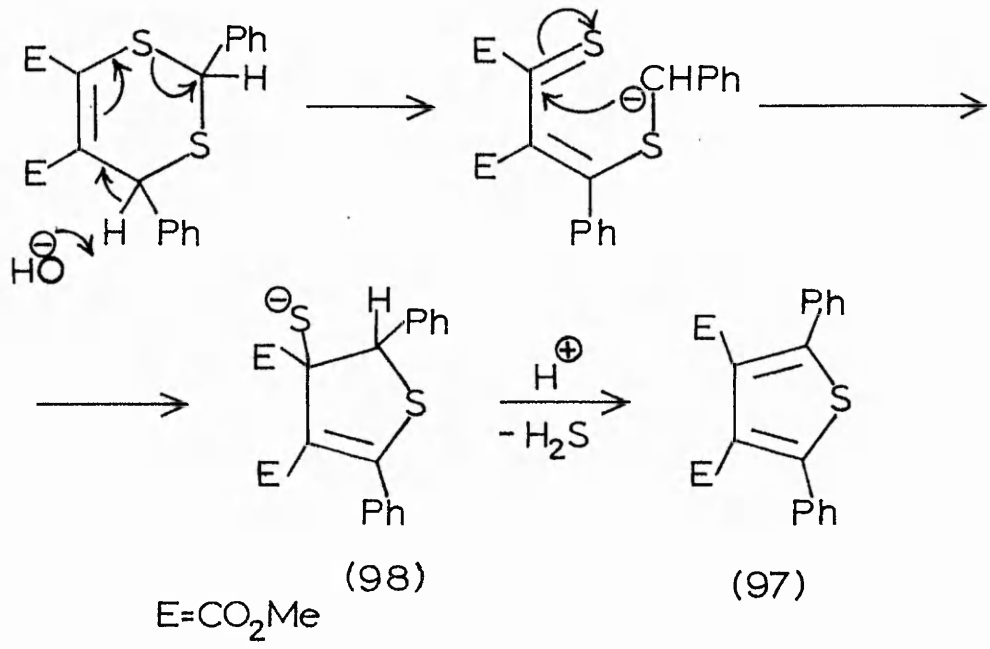


(70a) (97) $E = CO_2Me$

The product was isolated in fair yield (55%), and its identity was confirmed by a comparison of the spectroscopic data with literature[193] values. Identification of the other components in the mixture was not possible and none of the byproducts was soluble in sodium bicarbonate.

The same reaction took place in similar yield when a solution of the diester 70a in dichloromethane was treated with aqueous hydroxide in the presence of a phase-transfer catalyst. This useful modification to the reaction greatly facilitated the work-up procedure and cut the reaction time from 2 hours to 30 minutes.

A likely mechanism for this unusual reaction is as follows:



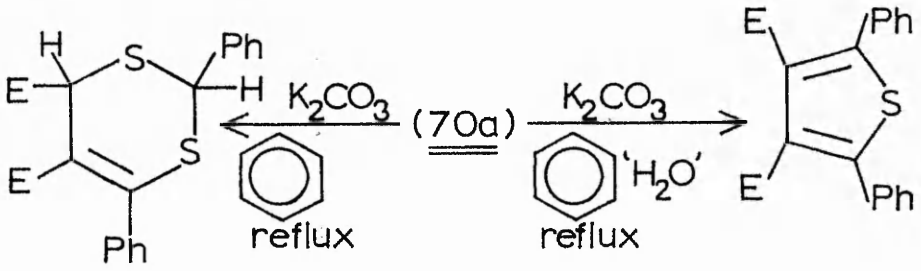
It is noticeable that this mechanism bears some resemblance to that postulated by Biellmann and Ducep[96] to explain the base catalysed rearrangement of thiacyclohexenes (see page 55). That the rearrangement is preferred to the hydrolysis of the ester groups is a reflection of the instability of this m-dithiin system, and an example of the ease with which m-dithiins extrude sulphur to form thiophens.

Attempts were made to glean information about the mechanism by the use of sodium deuteroxide as the base whilst monitoring the reaction in the probe of the nmr spectrometer. It was observed that almost as soon as the base was added, the two ester groups became magnetically equivalent. Detailed observation of the reaction was hindered, however, by rapidly changing peak definition which required constant tuning of the

spectrometer.

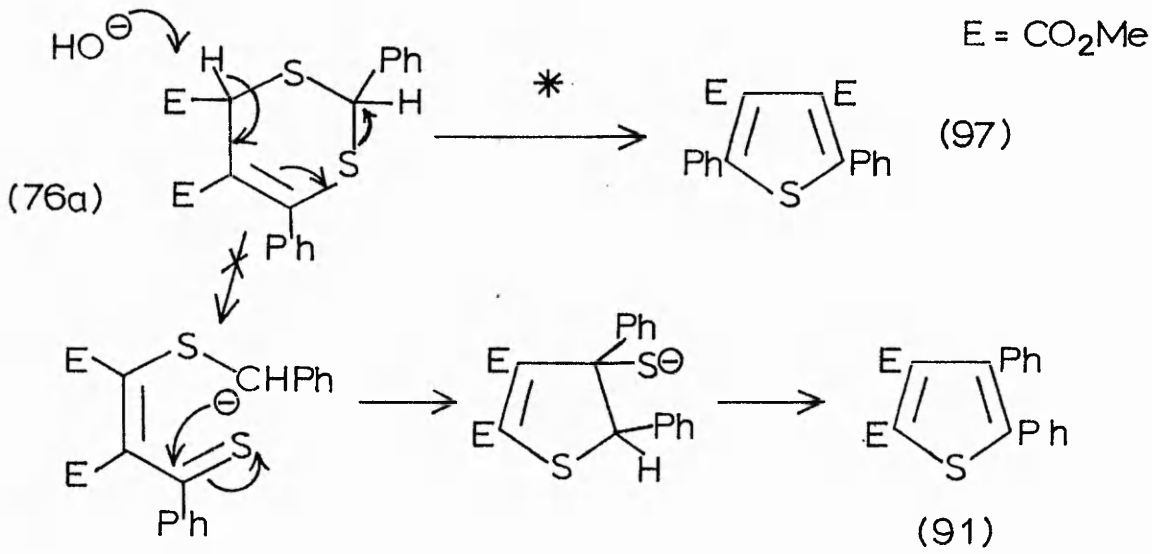
The contrast between the differing modes of action of base upon the m-dithiins was highlighted in one of the attempts to selectively abstract the C-4 proton by use of anhydrous potassium carbonate under phase-transfer conditions (see page 54). When inefficiently dried solvent was used the symmetrical thiophen 97 was formed in fair yield.

E = CO_2Me



(76a) (97)

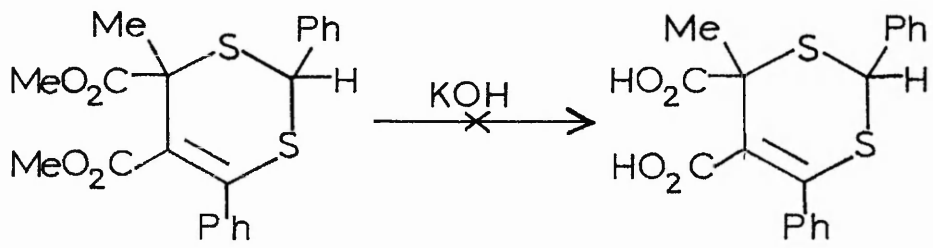
Evidence to support the proposed pathway in the sulphur extrusion is provided by the observation that the 6H-m-dithiin tautomer 76a also forms the symmetrical thiophen 97 when treated with aqueous hydroxide under phase-transfer conditions. The alternative pathway (shown below) leading to the unsymmetrical thiophen 91 is not observed. In this regard then, the 6H-tautomer 76a may be looked upon as an intermediate in the base catalysed sulphur extrusion from dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) (see page 77).



✳ pathway follows the same course as that for the 4H-tautomer, 70a, page 78.

When methyl iodide was included in the reaction mixture (under phase-transfer conditions) a slightly cleaner reaction was noted. This may be attributed to the methylation of the thiolate intermediate, 98, rendering it a more efficient leaving group in the elimination to give the symmetrical thiophen, 97.

The reaction of these m-dithiins with base, either under hydrous or anhydrous conditions has now been shown to proceed via the removal of the allylic proton. It would seem reasonable, therefore, to expect that if this proton were replaced by a methyl group, then some measure of stability to base would be conferred on the system thus enabling the ester groups to be hydrolysed. Contrary to expectations, however, it was found that no hydrolysis occurred. Instead, a complex mixture was obtained from which no product could be isolated.



(76c)

Following the failure to produce m-dithiin diacids using base hydrolysis, several other methods were used and the results are summarised in Table 4. No evidence of ester hydrolysis was observed in any of the reactions, and it is striking that the system is extremely stable to acid, and sensitive to basic conditions.

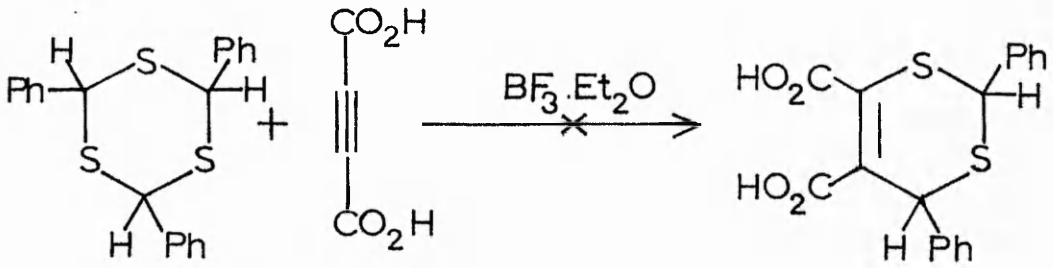
TABLE 4.

Attempted hydrolysis of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)

Reagent	Solvent	Time,h	Temp.°C	Remarks	Ref.
HCl	-	1.0	100	No reaction	138
H_2SO_4	-	0.2	50	No reaction	
HCO_2H	-	3.0	100	No reaction	140
NH_4OH	-	0.3	22	Decomposition	
Me_3SiI	$CHCl_3$	6.0	60	No reaction	141
KSCN	DMF	1.0	100	Decomposition	142
NaSPh	DMF	1.5	35	Mixture formed	143

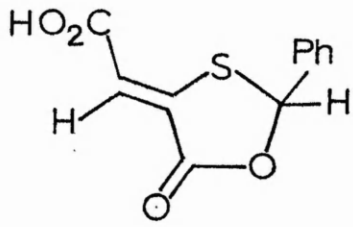
ii. Acetylenic diacid cyclisation

As an alternative approach to the synthesis of the m-dithiin diacid, 96, it was decided to attempt to cyclise acetylenedicarboxylic acid with 2,4,6-triphenyl-1,3,5-trithiane directly, using the method by which the esters 70a-e were formed. Acetylenedicarboxylic acid is insoluble in benzene and in toluene, and so acetonitrile was used as the solvent.

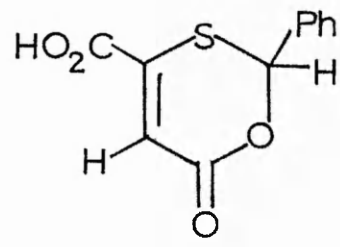


(96)

An acidic crystalline compound was obtained from the reaction, but spectroscopic analysis indicated that it was not the desired diacid. On the basis of nmr and microanalytical data, the two structures shown below were reasonable alternatives for the product.



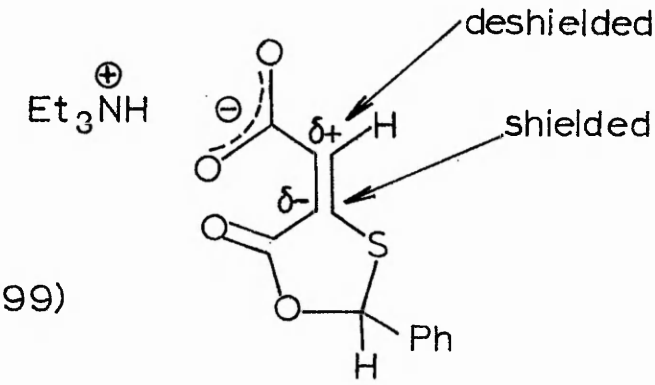
(99)



(100)

The ir carbonyl stretching frequency ($1770cm^{-1}$) is indicative of a five-membered lactone[144]; that in a six-membered lactone such as 100 would be expected to absorb at ca. $1685cm^{-1}$. Examination of the two structures reveals that the main difference between them is that in the five-membered ring, 99, the acid function and the vinylic proton have a geminal relationship, whereas in the six-membered ring they are vicinal.

The method used to assign the structure of the unknown compound has already been mentioned (see page 56). The acid was treated with triethylamine in DMSO, and the ^{13}C shifts induced in the α and β carbon atoms by the formation of the carboxylate anion were measured relative to those of the free acid. Examination of a range of acrylic acids in the same way, revealed that the α carbon was deshielded, and that the β carbon was shielded on salt formation. In the unknown compound, the carbon carrying the vinylic proton was deshielded, indicating that it occupies an α position with respect to the carboxylate carbon, and that the fully substituted carbon was shielded indicating that it occupies a β position. This proves conclusively that the lactone has the five-membered ring structure, 99.

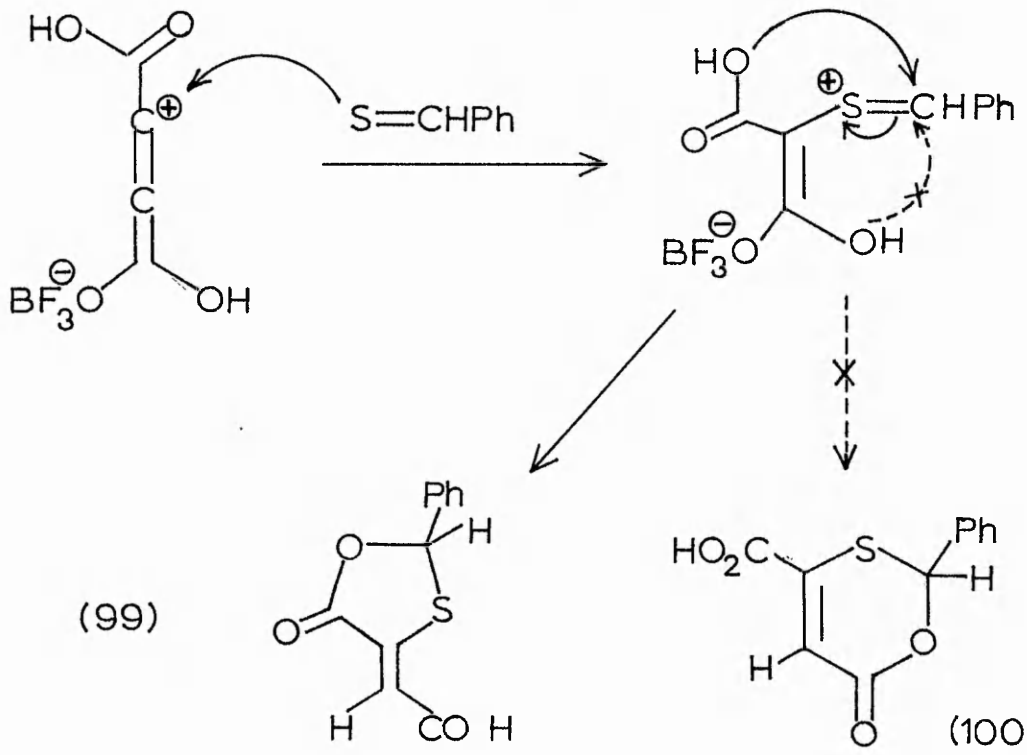


(99)

Infrared spectroscopic studies on solutions of varying concentration suggested that the five-membered lactone exists as an intermolecularly hydrogen-bonded dimer.

A detailed analysis of this spectroscopic study (complete with ^{13}Cnmr data for standard acrylic acids) is presented in Appendix B.

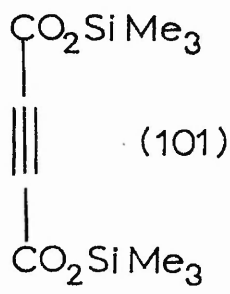
The pathway leading to this novel cyclic lactone may be expressed in the following way:



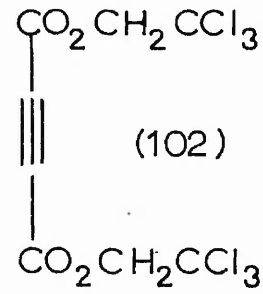
(99) (100)

It was clear then, that in order to cyclise acetylenedicarboxylic acid in the correct way to obtain m-dithiins, the acid function would have to be protected by a group which could easily be removed from the product m-dithiin.

With this objective in mind, attempts were made to form di-t-butyl acetylenedicarboxylate. Unfortunately, none of the desired product could be obtained using the methods available. It was possible, however, to prepare two new acetylenic diesters, namely, bistrimethylsilyl acetylene-dicarboxylate, (101) and bis-2,2,2-trichloroethyl acetylenedicarboxylate (102).



(101)

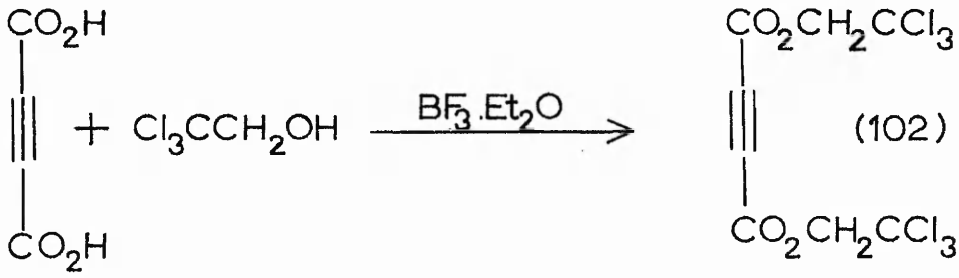


(102)

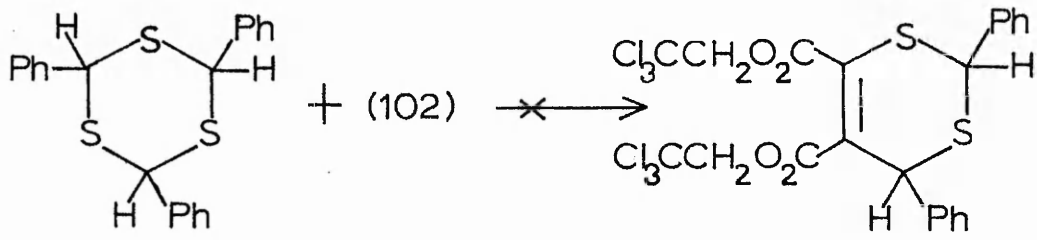
The silyl ester, 101, prepared using N-trimethylsilyl acetamide, was found to be extremely air- and moisture-sensitive. In fact its great reactivity precluded its use in the cyclisation reaction, since decomposition took place long before reaction with the trithiane.

The trichloroethyl diester, 102, was prepared by the boron trifluoride-catalysed esterification of

acetylenedicarboxylic acid with 2,2,2-trichloroethanol.



Unfortunately, the cyclisation of the acetylenic diester, 102, with 2,4,6-triphenyl-1,3,5-trithiane could not be achieved. Under various conditions none of the trithiane was consumed in the reaction.

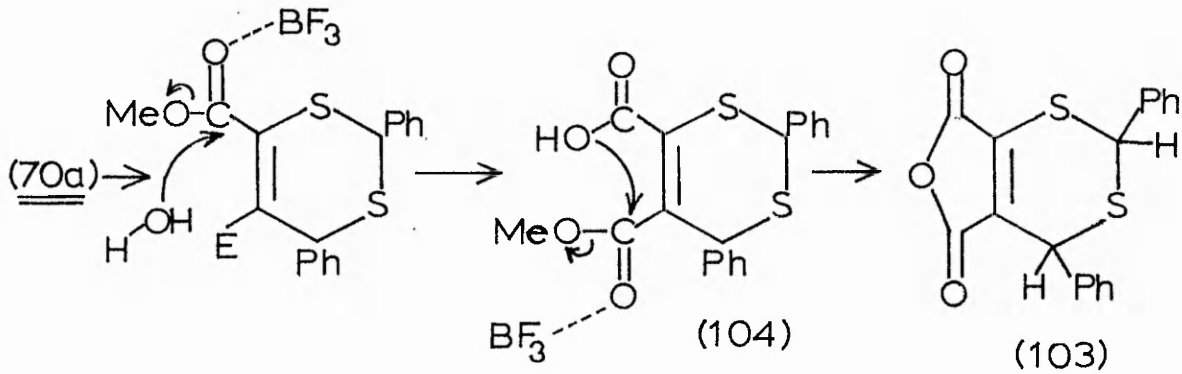


iii. Anhydride formation

Success in forming 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylic acid (96) eventually came when the parent diester 70a was heated under reflux in toluene containing one molar equivalent of water in the presence of boron trifluoride etherate. This led to a high yield of the anhydride, 103, from which the diacid 96 was prepared by standard methods. On moderate heating, the diacid 96 reverted to the anhydride 103.

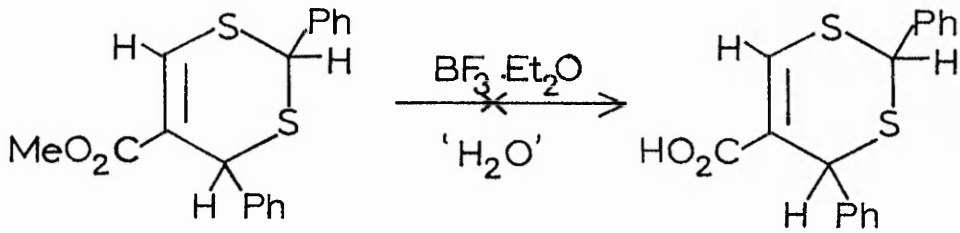
When dry toluene was used as the solvent, the

only reaction which took place was the gradual thermal rearrangement to the corresponding o-dithiin (see later; page118). The observation that an equivalent of water is necessary, indicates that the reaction must involve the formation of the half-ester, 104, as shown below.



The formation of an anhydride from a vicinal diester on treatment with boron trifluoride etherate is not peculiar to m-dithiin diesters. Thus, when di-n-butyl phthalate was treated in the same way, phthalic anhydride was obtained in good yield.

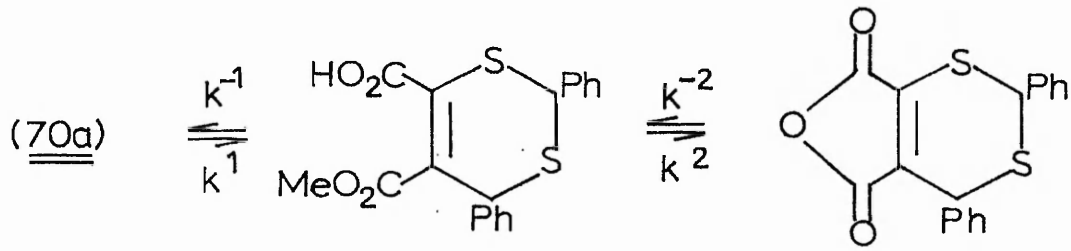
The presence of a vicinal ester group is normally required for an efficient reaction; when methyl benzoate was treated as above, only 7% benzoic acid was isolated after several hours' reflux. Similarly, very little change was observed when methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b) was treated with boron trifluoride in the same way.



(70b)

When dimethyl maleate was treated in this way, however, no reaction occurred despite the presence of vicinal ester groups. Thus, the cyclic system, whether aromatic or heterocylic must confer considerable stability during the reaction.

It would seem that the reaction can be represented by the following equilibria:



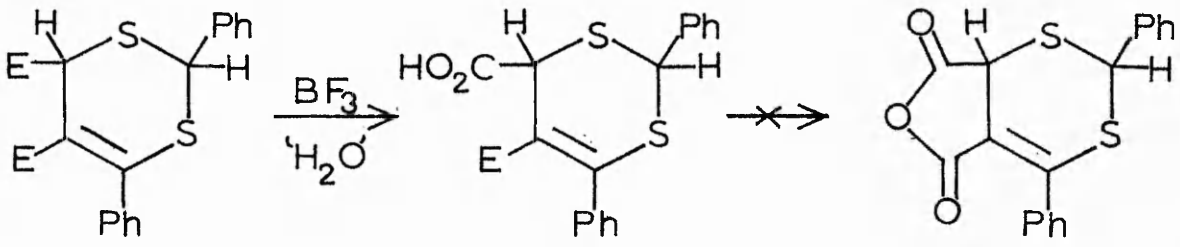
(104) (103)

$k^2 \gg k^{-1}$

The presence of the double bond between the ester groups is also very important; when m-dithiin 76a (6H-tautomer of 70a) was treated with boron trifluoride in refluxing toluene with an equivalent of water present, only the half-ester, 105, was isolated. Spectroscopic evidence indicated that this was 5-methoxycarbonyl-2,4-

diphenyl-6H-m-dithiin-6-carboxylic acid rather than the alternative half-ester, 84, (which had previously been prepared by the reaction of diester 70a with n-butyllithium in the presence of DABCO, followed by water; page 56).

E = CO_2Me

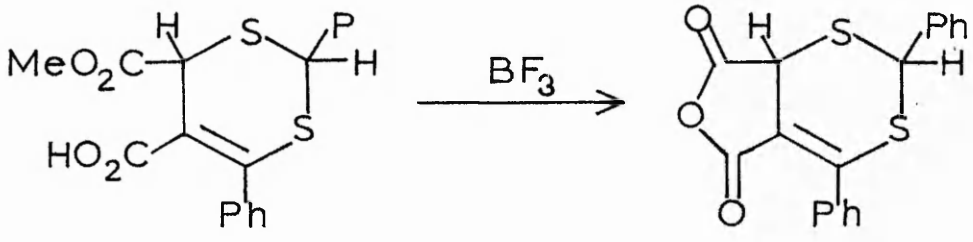


(76a) (105) (106)

The nonconjugated anhydride, 106, was isolated in low yield when the half-ester, 84, was treated with boron trifluoride.

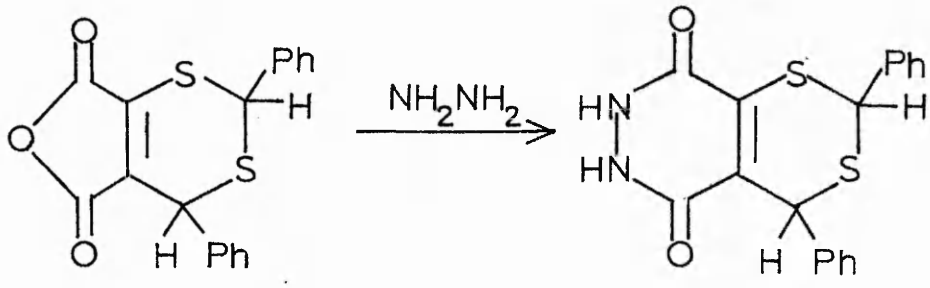
Having established a convenient method for functionalising the C-5 and C-6 positions in the m-dithiins through anhydride formation, many possibilities for further reaction present themselves.

The conjugated anhydride, 103, when treated with hydrazine gave the hydrazo-dione type derivative, 107, as shown below.

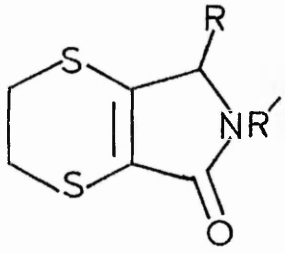


(84) (106)

Unfortunately, lack of time precluded the synthesis of other fused heterocyles from the anhydride, but no problems are envisaged in the formation of these and other similar compounds which by analogy with p-dithiins such as 14[33-35], may possess some interesting biological activity.



(103) (107)



R, R' = alkyl

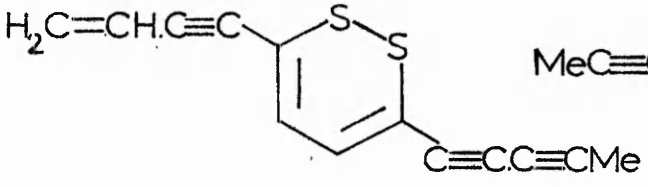
(14)

o-DITHIINS

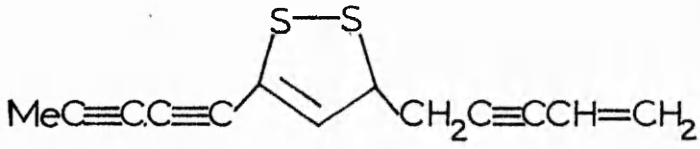
PART 1. INTRODUCTION

A. Anhydro o-dithiins

In contrast to the m-dithiin series, most of the reported work on o-dithiins has taken place since the mid-1960's. In 1964, Mortensen et al[145] isolated an acetylenic disulphide from Eriophyllum pigments. They proposed the o-dithiin structure, 108, but could not exclude the possibility that the compound was the 1,2-dithiole, 109.

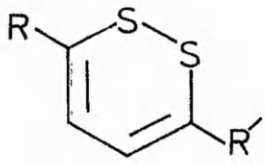


(108)

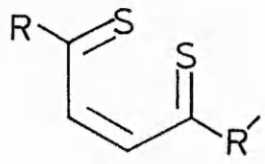


(109)

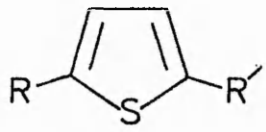
Bohlmann and Kleine[146], the following year, extracted a red oil from Heliantheae, Helenieae plants, and suggested the valence tautomeric structures 110 or 111 for the compound. Spectroscopic data were reported, and a comparison with later findings[10,11] indicates that the o-dithiin structure, 110, is the more likely. When 110 was briefly heated at 80° under reduced pressure, the thiophen 112 and sulphur were formed; the same reaction took place on irradiation with uv light. The same thiophen (112) and mercuric sulphide were formed when an ethereal solution of the disulphide was stirred with mercury.



(110)



(111)

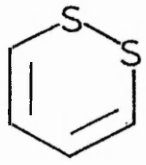


(112)

R = C≡CCH=CHCH=CH$_2$

R′ = C≡CMe

In 1965, Schroth, Billig and Zschunke[3] obtained the parent unsubstituted o-dithiin, 2, as orange-red crystals by treating cis, cis-dimercaptobutadiene in methanol with iron (III) chloride.

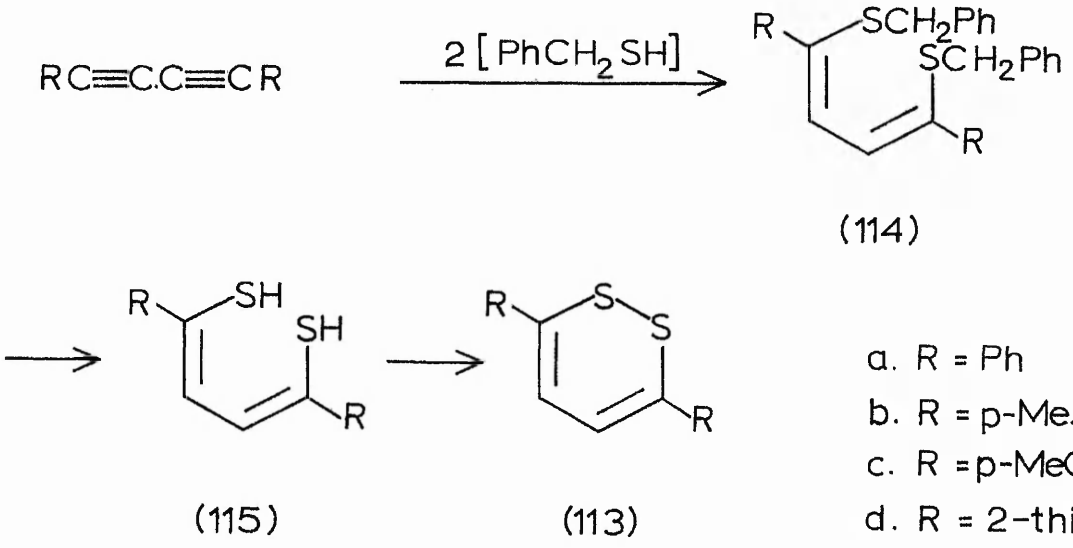


(2)

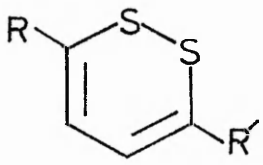
Treatment with sodium in liquid ammonia gave the sodium salt of dimercaptobutadiene, and it was concluded from the extraordinary lability to alkali and the ^{1}Hnmr spectrum (which consisted of a quartet at δ5.37 and a doublet at 6.13ppm; J$\sim$9Hz), that the compound was nonaromatic. Sulphur extrusion occurred

readily, producing thiophen[147], and polymerisation.

Schroth and co-workers[3] have synthesised 3,6-disubstituted o-dithiins 113a-d by a sequence which involved firstly the nucleophilic addition of benzyl mercaptan to butadiynes (which afforded cis, cis-1,4-bis(benzylthio)butadienes, 114a-d), followed by reductive debenzylation of 114a-d with sodium in liquid ammonia (giving the cis, cis-1,4-dimercapto-butadienes, 115a-d). Finally, aerial oxidation in alkaline solution yielded the desired products 113a-d.



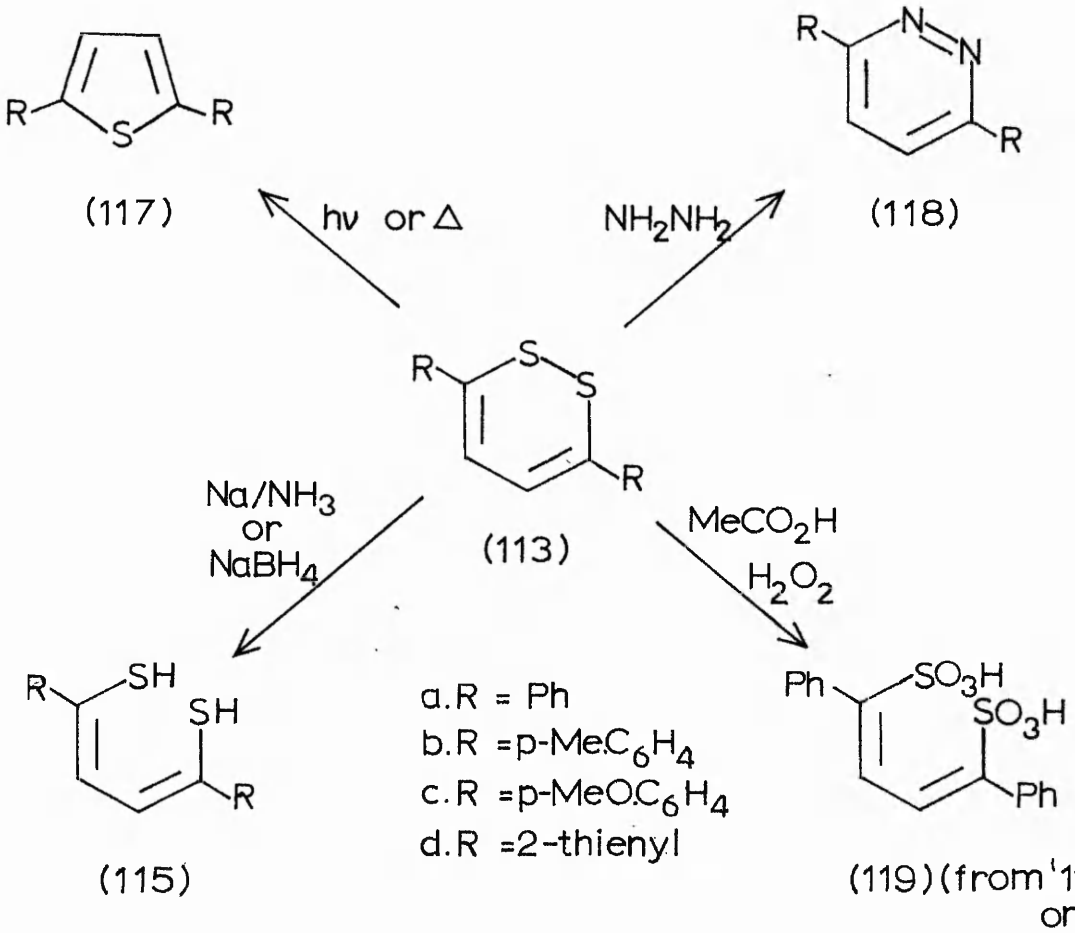
In a later publication, Schroth et al[148] reported the preparation of the o-dithiins 116a-e by a similar series of reactions.



(116)

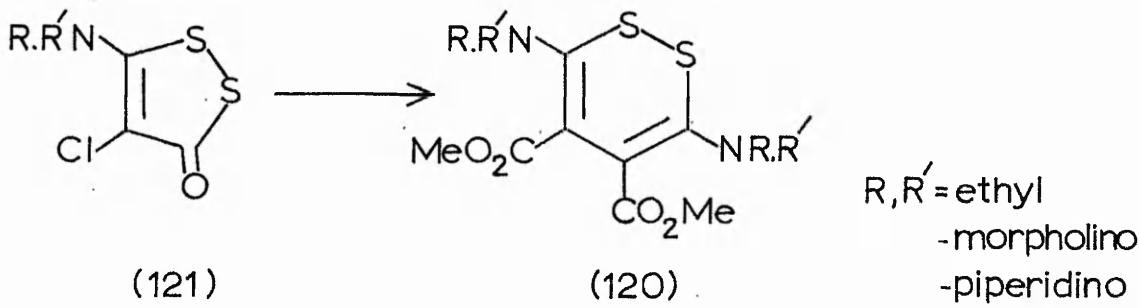
a. R = R′ = Me
b. R = Ph, R′ = p-Me.C$_6$H$_4$
c. R = Ph, R′ = p-MeO.C$_6$H$_4$
d. R = R′ = p-Ph.C$_6$H$_4$
e. R = R′ = α-naphthyl

The 3,6-disubstituted o-dithiins 113a-d were reduced with sodium borohydride or sodium in liquid ammonia to give the dithiols 115a-d. On heating or uv irradiation the former also extruded sulphur to yield the 2,5-disubstituted thiophens 117a-d, and when reacted with hydrazine in pyridine or N,N-dimethylformamide, they formed the 3,6-disubstituted pyridazines 118a-d.



3,6-Diphenyl-o-dithiin (113a) was oxidised by hydrogen peroxide in glacial acetic acid to 1,4-diphenylbutadiene-1,4-disulphonic acid (119).

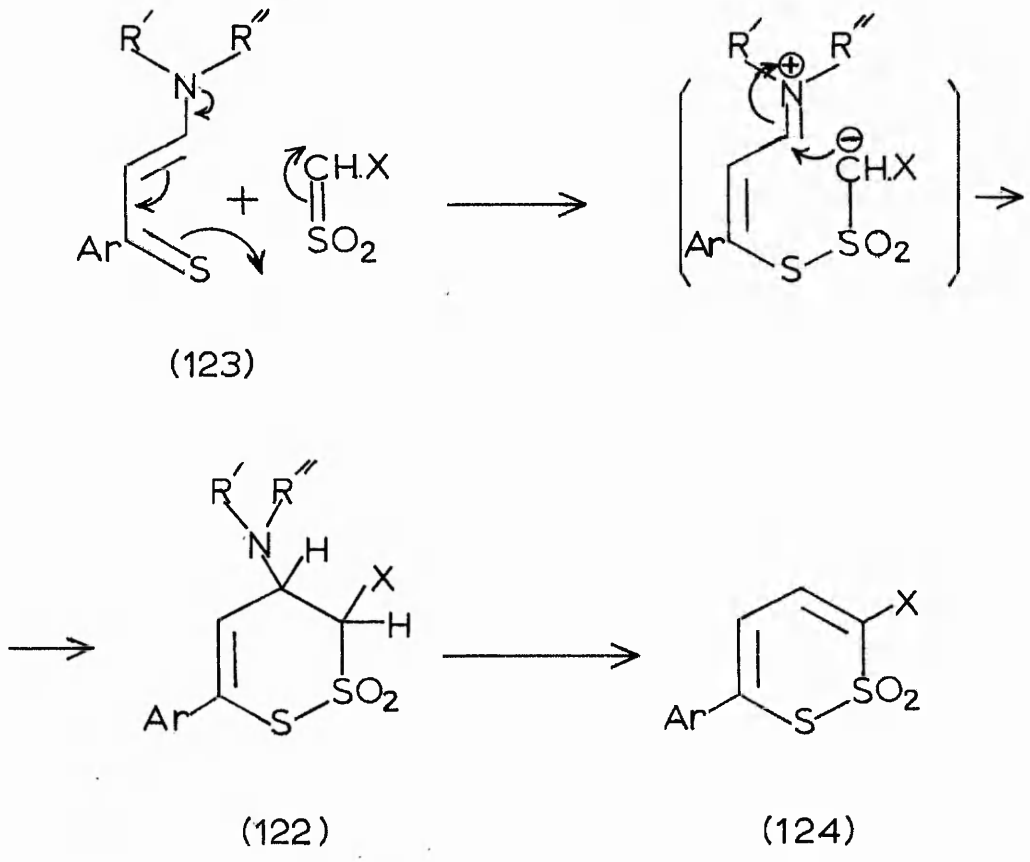
The 3,6-diamino-o-dithiin-4,5-dicarboxylic ester 120 was obtained by Boberg et al[149] by the ring expansion of the dithiole, 121, under the influence of methanolic hydrogen chloride. The structure was deduced from nmr data, but no mechanism for the reaction was



(121) (120)

suggested. This was the first synthesis of an o-dithiin carboxylic acid derivative.

Meslin et al[150,151] have prepared the substituted 3,4-dihydro-o-dithiin-2,2-dioxides 122 in 40-60% yields by the reaction of thioamide vinylogues 123 with sulphene.



(123)

(122)

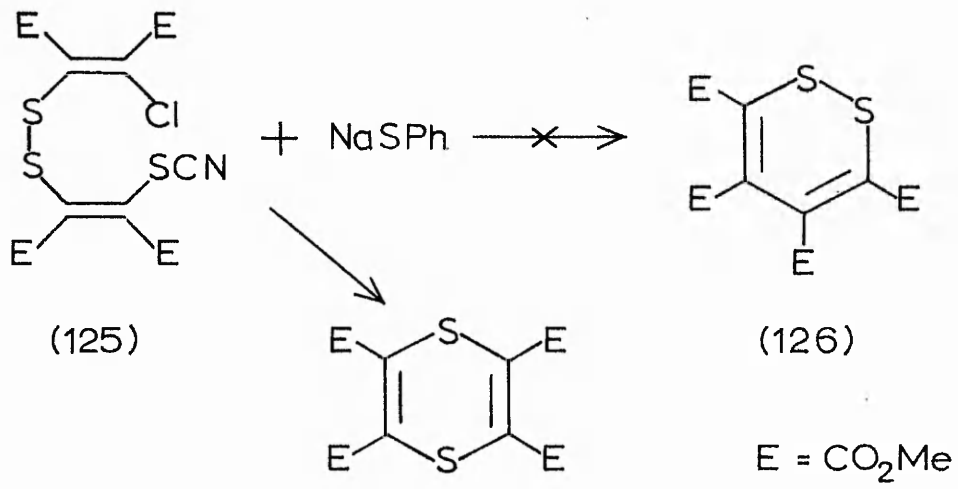
(124)

$NR'R''$ = morpholino; piperidino; o-anisidino

Ar = Ph; p-Br.C_6H_4; p-Me.C_6H_4; p-MeO.C_6H_4

When phenylsulphene was employed in the reaction, elimination of R'R''NH took place to give the anhydro-o-dithiin-2,2-dioxides, 124.

The reaction of the complex divinyl disulphide 125 with sodium thiophenoxide was reported[152] to give the tetrasubstituted o-dithiin, 126. Recently, however, it has been shown[153] (by ^{1}Hnmr, uv, ir and mass spectrometry) that this rather surprising result is incorrect; the

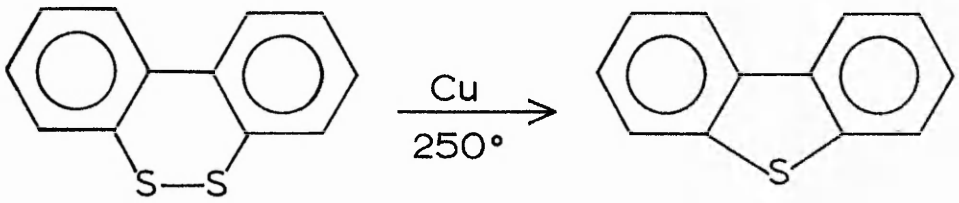


(125) (126)

(127)

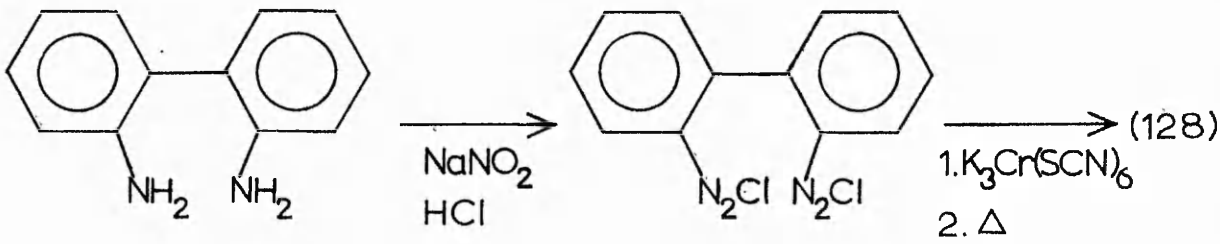
true nature of the product is the isomeric p-dithiin 127.

Dibenzo [c,e] -o-dithiin (128) was first isolated by Barber and Smiles in 1928[154]. These workers discovered that the compound readily lost sulphur when it was heated at 250°C in the presence of copper, forming dibenzothiophen.

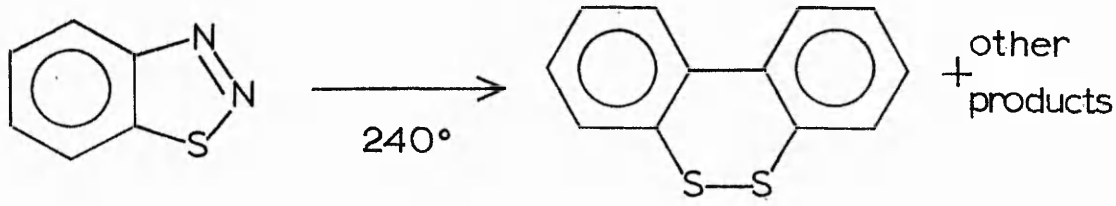


(128)

Dibenzo [c,e] -o-dithiin was also isolated as a byproduct when the 5,6-tetrazonium salt of 2,2'-diamino biphenyl was heated with $K_3Cr(SCN)_6$. The main product was dibenzothiophen[155].

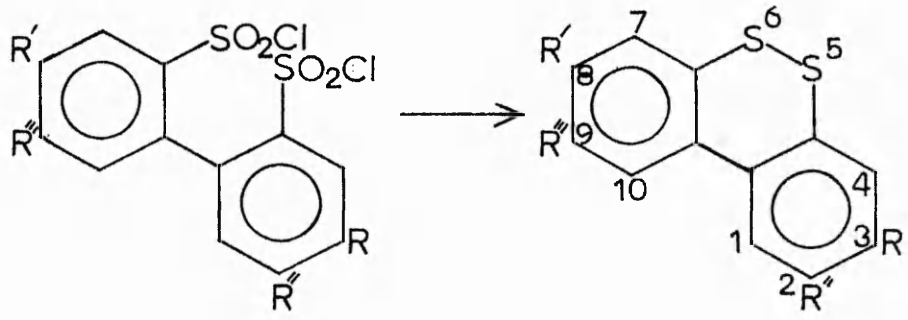


More recently 128 was obtained as a byproduct in the thermal Wolff rearrangement of 1,2,3-thiadiazoles[156].



(128)

In an alternative approach to the dibenzo [c,e] - o-dithiin system, Zheltov and coworkers[157] treated the bipheny1-2,2'-bis-sulphony1 chlorides 129a and b with hydriodic acid in acetic acid at room temperature.



(129) (130)

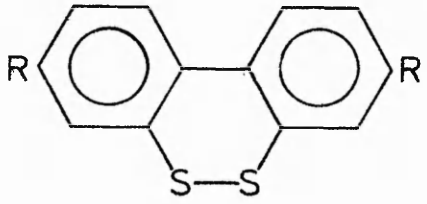
a. $R = R' = NO_2$; $R'' = R''' = H$
b. $R = R' = H$; $R'' = R''' = NO_2$
c. $R = NO_2$, $R' = NH_2$; $R'' = R''' = H$
d. $R = R' = NH_2$; $R'' = R''' = H$
e. $R = R' = H$; $R'' = NO_2$, $R''' = NH_2$
f. $R = R' = H$; $R'' = R''' = NH_2$

When 130a was reduced with 55% hydriodic acid, 8-amino-3-nitrodibenzo [c,e] -o-dithiin (130c) was obtained, together with minor amounts of 3,8-diaminodibenzo [c,e] -o-dithiin (130d)[158]. The proportion of 130d in the product increased with increasing concentration of hydriodic acid; however 130d was the major product when the reduction of 130a was carried out with tin (II) chloride and hydrochloric acid.

9-Amino-2-nitrodibenzo [c,e] -o-dithiin (130e) and 9,2-diaminodibenzo [c,e] -o-dithiin (130f) have been prepared[159] by the reduction of 2,9-dinitrodibenzo [c,e] -o-dithiin (130b) with sodium bisulphite.

Diazotization of 8-amino-3-nitrodibenzo [c,e] -o-dithiin (130c) and replacement of the diazonium group by

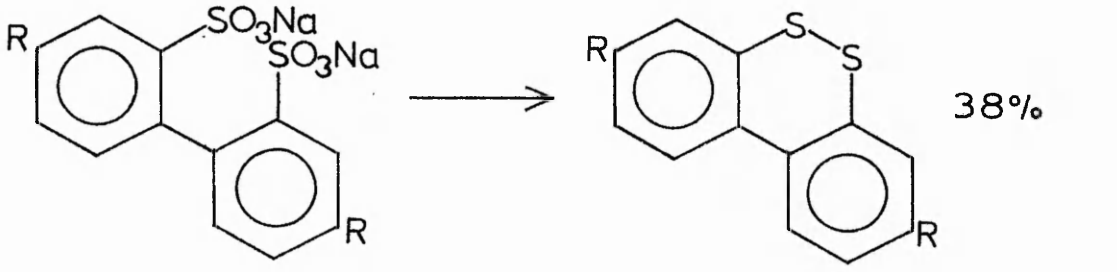
various substituents led to the synthesis of seven substituted o-dithiins 131. The acetyl derivatives of the o-dithiins 130e and f and 131 were also described.



$R = NO_2, NH_2,$ Cl, I, H

(131)

3,8-Diaminodibenzo [c,e] -o-dithiin (130d) has been prepared[160] by reaction of the sodium salt of 3,8-diaminobiphenylene-5,6-disulphonic acid (132) with chlorosulphonic acid below -10°, followed firstly by heating at 85° for 8 hours, then by treatment with 55% hydriodic acid at 60°.

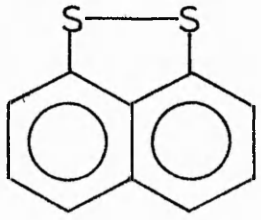


(132) (130d) $R = NH_2$

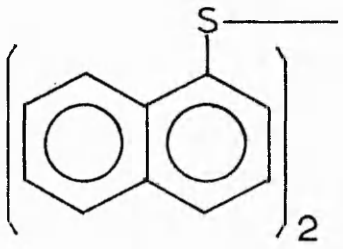
The uv spectra of several of the above dibenzo [c,e] -o-dithiins have been correlated with the structures given[161].

A comparison has been made by Peduli et al[13] of some of the electrophilic reactions of dibenzo [c,e] -o-

dithiin, (128), napthalene-1,8-disulphide (133), and the acyclic dinapthyl disulphide, 134. Oxidation (with perbenzoic acid) and bromination reactions were studied, and the results



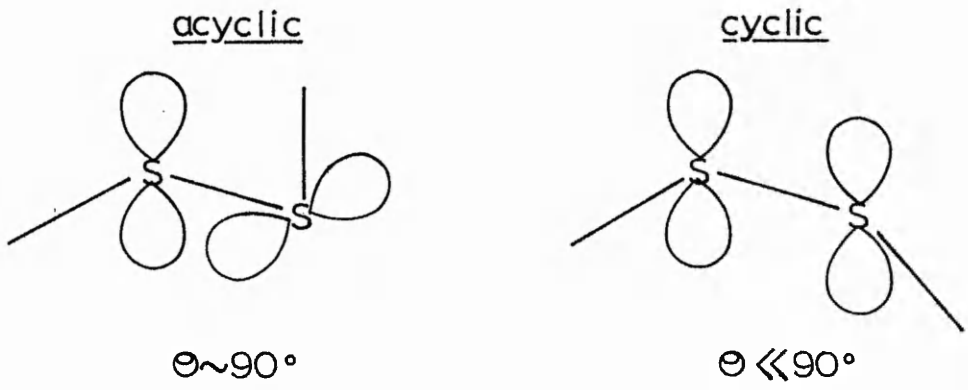
(133)



(134)

serve to illustrate some of the fundamental differences between the three systems.

In the oxidation experiments, the cyclic disulphides gave firstly thiolsulphinates (monosulphoxides) then thiolsulphonates (monosulphones) in high yield, whereas the acyclic dinaphthyl disulphide gave mixtures of mono- and dioxides. This can be explained by the fact that the cyclic disulphides are strained systems in which there is considerable repulsion between the non-bonding p orbitals on the sulphur atoms. When sulphoxide formation occurs, these p orbitals are utilised, and the strain is thus reduced. In the acyclic disulphide, the C-S-S-C dihedral angle, Θ , is approximately 90^{o}, allowing orthogonality between the non-bonding p orbitals; in this case therefore, sulphoxide formation does not result in reduced repulsion, since this is already at a minimum.

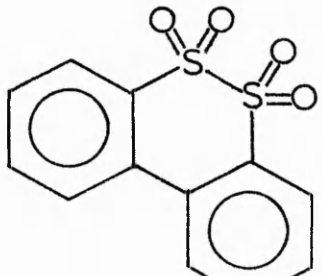


The acyclic dinaphthyl disulphide (134) and the cyclic naphthalene-1,8-disulphide (133) were readily brominated in the para position, but dibenzo [c,e] -o-dithiin (128) did not react. It was suggested that this was due to the geometry of the fused o-dithiin, which restricts electronic interactions between the sulphur atoms and the aromatic rings.

The same workers also made a study of the esr spectra from the cation radicals produced by oxidation of the systems in concentrated sulphuric acid. The result (which has already been discussed on page 4) confirms the above observation that delocalisation between the non-bonding electrons on sulphur and the aromatic rings is minimal for fused o-dithiins such as 128.

Chau and Kice have published a series of papers[162-164] concerning the formation of dibenzo [c,e] - o-dithiin S-oxidation products at all levels of oxidation. The reactivity of the variously oxidised substances was studied (particularly towards nucleophilic attack), and was compared with that of other cyclic and acyclic

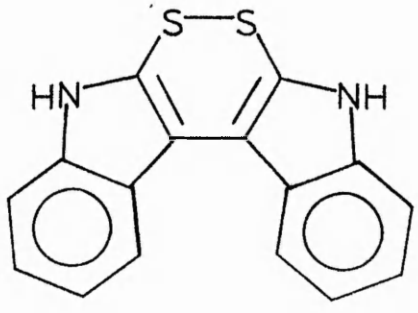
disulphides. Interestingly, it was found that fused o-dithiin disulphones such as 135 were slower to react with nucleophiles than their less strained acyclic analogues. This is presumably due to the steric restraint imposed on the attacking nucleophile in the cyclic system.



(135)

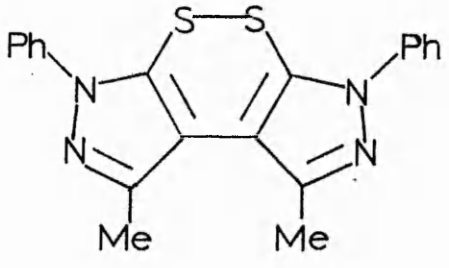
Dibenzo [c,e] -o-dithiin-5,5-dioxide, when treated with nucleophiles such as cyanide or sulphite, formed biphenyl cyanates and Bunte salts respectively. These,however, rapidly and quantitatively reverted back to the o-dithiin-5,5-dioxide on treatment with acid.

As in the m-dithiin series (see page 23), fused heterocyclic derivatives of o-dithiins have been prepared; these include o-dithiino-indole 136[165] and o-dithiino-diazole 137[166].



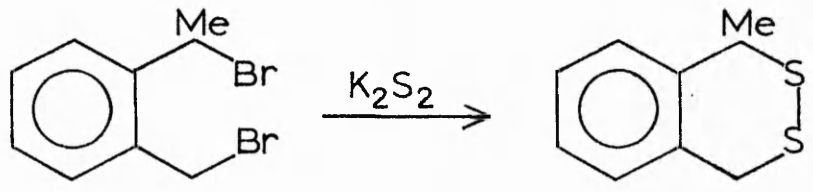
(136)

(137)



B. Dihydro o-dithiins

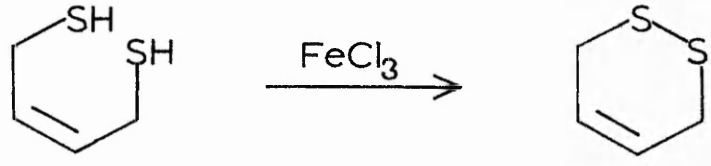
In 1929, Von Braun and Weissbach prepared 3-methyl-benzo[d]-o-dithiin (139) by the reaction of the dibromide 138 with potassium disulphide[167]. The product had a melting



(138) (139)

point of 40° and darkened on standing. None of its reactions was investigated.

Almost thirty years later, Schöberl and Grafje[15] isolated, in poor yield, the parent unsubstituted 3,6-dihydro-o-dithiin (8) by the oxidation of cis-1,4-dimercaptobut-2-ene with iron (III) chloride. The yield was improved to 70% by Lüttringhaus et al[66], who isolated 8 in a pure state as a yellow oil. The product polymerised on standing however, and was found[15] to be much more reactive towards nucleophiles such as cyanide ion than the fully

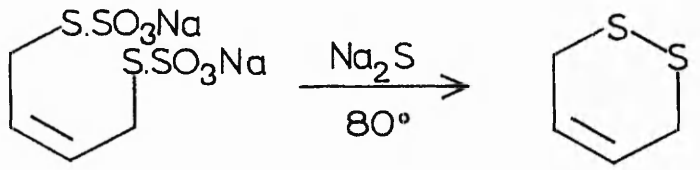


(8)

saturated o-dithiane. The products of the reaction of 8

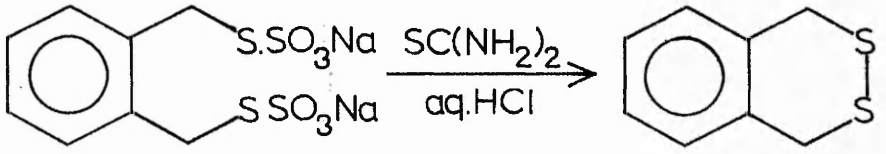
with cyanide ion were shown by Everhardus et al[168] to be 2-vinylthiirane and 2,5-dihydrothiophen.

Rosenthal[169] later prepared 8 by heating the Bunté salt 140 with sodium sulphide at 80°. The product formed a dark grey rubbery polymer after a few days at room temperature.



(140) (8)

A similar method had already been used by Milligan and Swan[170], who synthesised benzo [d] -o-dithiin (7) by reacting the Bunté salt 141 with thiourea in hot dilute hydrochloric acid. The methylene protons of 7 were shown

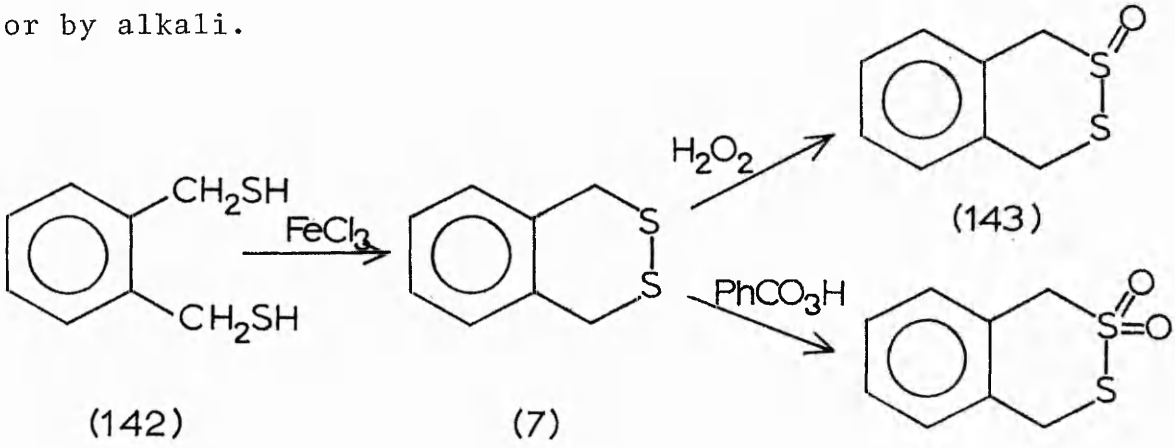


(141) (7)

to be equivalent in the nmr spectrum, even at low temperatures, reflecting the ease with which inversion of conformation occurs. This is probably due to the relatively small C-S-S-C dihedral angle (~45°) compared with that of o-dithiane (60°).

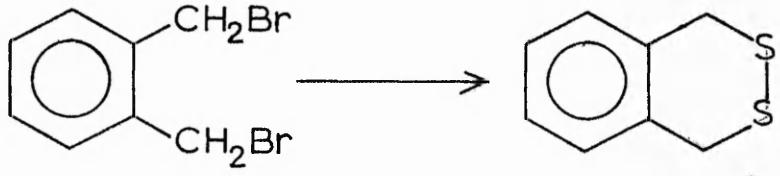
The first preparation of benzo [d] -o-dithiin (7) had taken place some years earlier, when Lüttringhaus and Hagele[14] oxidised the benzo-dithiol 142 with iron (III)

chloride in acetic acid. They found the product to have properties consistent with a disulphide, and prepared the 1-oxide 143 and 1,1-dioxide, 144. Benzo[d]-o-dithiin (7) had a melting point of 80°, possessed the odour of naphthalene, and was readily decomposed photochemically or by alkali.



(142) (7) (143) (144)

A third method has been used to prepare benzo[d]-o-dithiin (7); the dibromide 145 was treated[171] with thiourea followed by sodium hydroxide, then iron (III) chloride. The spectroscopic data were in agreement with those reported previously.

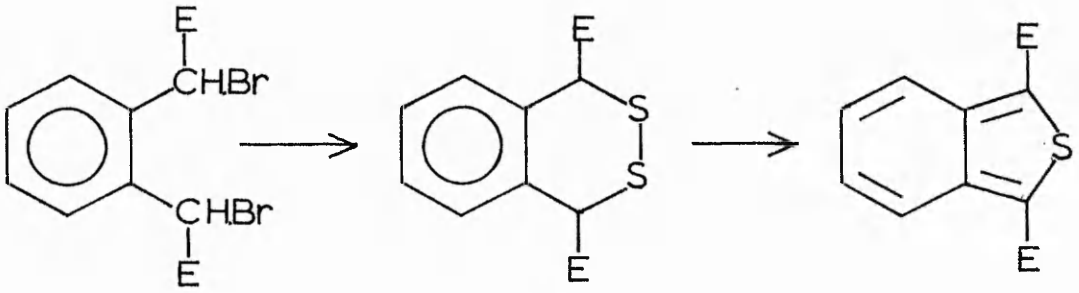


(145) (7)

The preparation of 3,8-dimethoxycarbonyl-benzo[d]-o-dithiin (147) and its decomposition to the thiophen, 148, have been described by Cignarella and Cordella[172]. The o-dithiin 147 was prepared from 146 by the method of Von Braun[167], and the sulphur extrusion

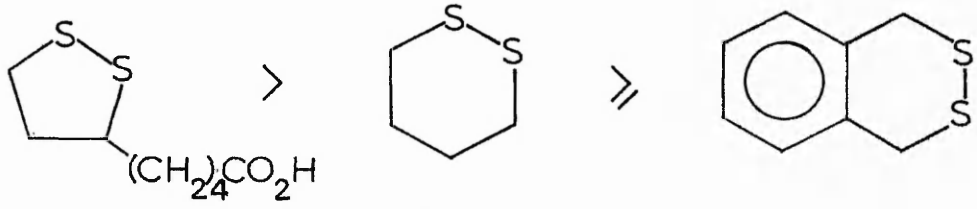
took place readily in alcoholic sodium methoxide at 0° or in refluxing methanol. It was stable under reflux in acidic methanol or benzene, however, and decomposition occurred very slowly in aqueous alkali.

E = CO_2Me



(146) (147) (148)

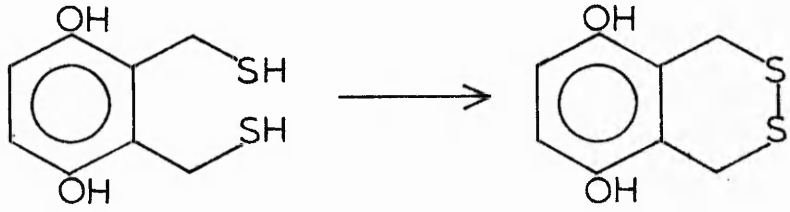
Hudson and Fillipini[16] have related the reactivity of cyclic disulphides such as benzo [d] -o-dithiin (7) to the C-S-S-C dihedral angle, Θ . Their criterion was the rate of reaction with methylating agents such as 'magic methyl' ($MeSO_3F$), and dimethyl sulphate, and they found that the following rate order was observed:



(10) (7)

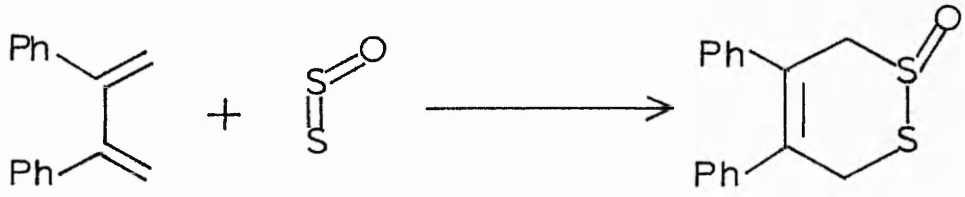
The order was explained in terms of the lone pair-lone pair repulsion of the sulphur atoms arising from the decreasing C-S-S-C dihedral angle, but there is an apparent anomaly here, because the dihedral angle of benzo [d] -o-dithiin (~45°) is smaller than that of o-dithiane (~60°).

Fields and co-workers[173] isolated 4,7-dihydroxybenzo [d]-o-dithiin (150) by titration of the dithiol, 149, in ether with 0.1 N iodine solution containing an equivalent of pyridine (used as a hydrogen iodide scavenger). The diacetate of 150 was also described.



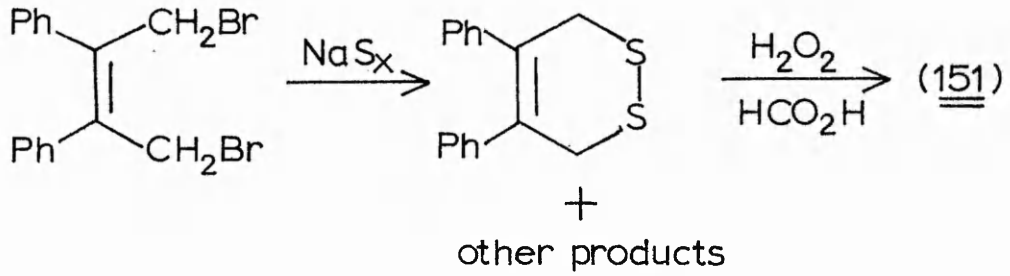
(149) (150)

The possibility of synthesising an o-dithiin by a (4 + 2) π electron cycloaddition reaction was examined by Dodson and coworkers[39]. In the event, 3,6-dihydro-4,5-diphenyl-o-dithiin-1-oxide (151) was only inefficiently produced by the interaction of 2,3-diphenylbutadiene and disulphur monoxide.



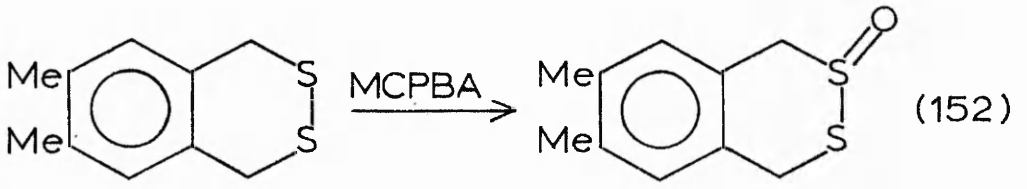
(151)

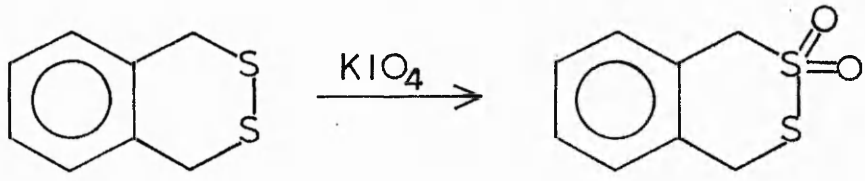
In order to confirm the identity of the product, 151 (which is reported to have bactericidal and fungicidal properties), the independent synthesis illustrated below was carried out:



The product was unstable, decomposing to 2,3-diphenylbutadiene on contact with water, or on warming.

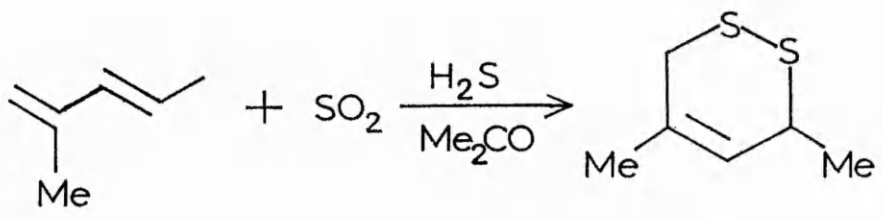
Several fused dihydro o-dithiins have been successfully oxidised; 5,6-dimethyl-benzo [d] -o-dithiin formed the monosulphoxide, 152, when treated with MCPBA[174], and benzo [d] -o-dithiin gave the monosulphone, 144, with potassium periodate[171].





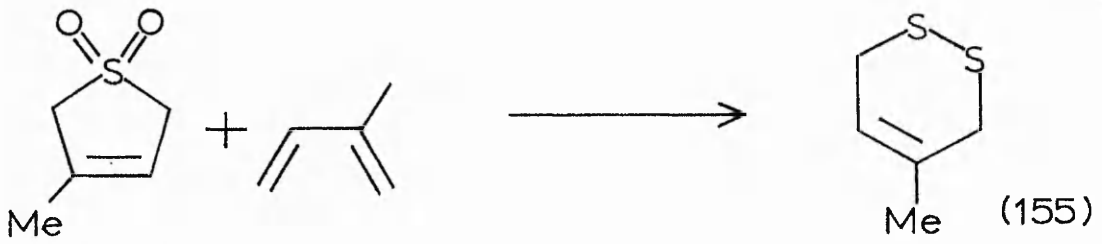
(144)

Payne[175] reacted 2-methyl-1,3-pentadiene (dissolved in acetone containing hydrogen sulphide and catalytic amounts of hydroquinone and water) with sulphur dioxide under pressure at 140°. Thus was obtained, a rather poor yield (20%) of 3,5-dimethyl-3,6-dihydro-o-dithiin (154).



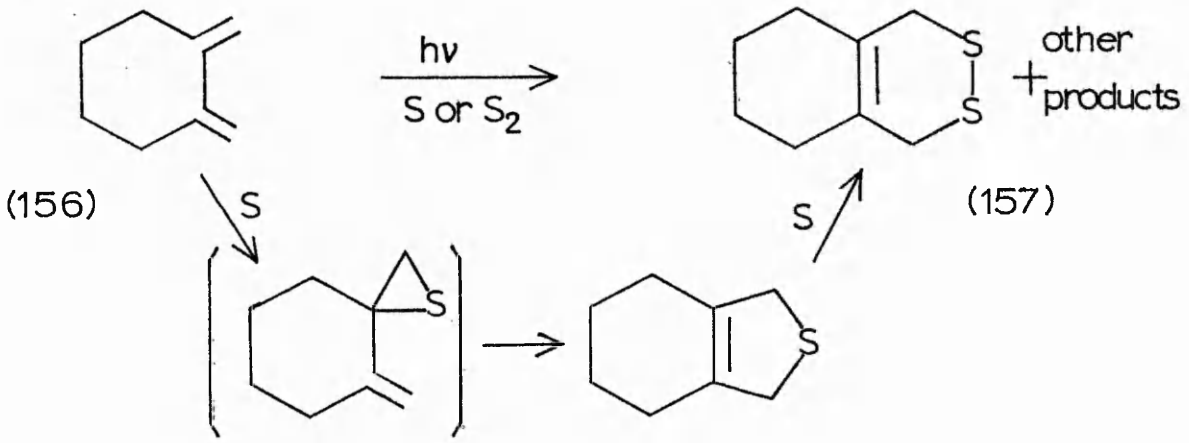
(154)

Under similar conditions, 3-methyl-3-sulpholene (153) and isoprene in acetone afforded 4-methyl-3,6-dihydro-o-dithiin (155).

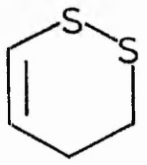


(153) (155)

The addition of photochemically produced sulphur to 1,2-methylenecyclohexane (156) has been reported by Jahn and Schmidt.[176] One of the products was identified as the tetrahydrobenzo [d] -o-dithiin, 157, but this was not accepted as unambiguous evidence that diatomic sulphur was the attacking species. It was suggested that 157 could also have been formed by the addition of monoatomic sulphur in the way shown below. The same dihydro-o-dithiin, 157, was independently synthesised from the corresponding dithiol using methods already described[15].

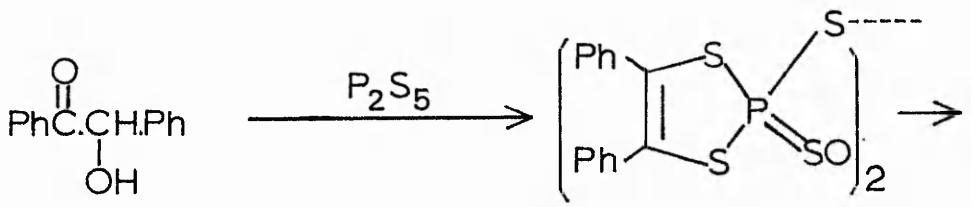


The 3,4-dihydro-o-dithiins represent by far the rarest of the dithiin species, and the unsubstituted parent compound 9 is unknown.

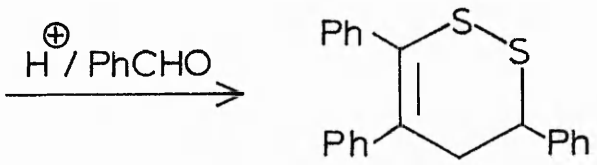


(9)

The formation of a substance believed to be 3,4-dihydro-3,5,6-triphenyl-o-dithiin (158) has been reported by Schrauzer and co-workers[177]. On heating benzoin with phosphorus pentasulphide in an inert organic solvent, an amber resin ($C_{28}H_{20}O_5P_2O_2$) was formed; it was assigned the structure 159. Solvolysis of 159 in the presence of benzaldehyde gave a compound which was formulated as 158 in spite of inconsistent microanalytical data. No proof of structure was offered.

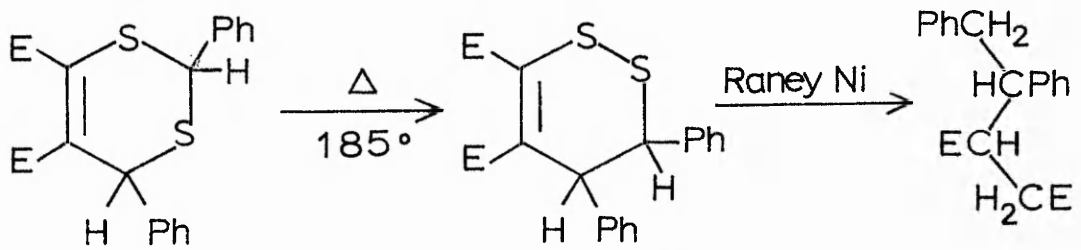


(159)



(158)

Eisner and Krishnamurthy[71] have reported the facile thermal rearrangement of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) to the corresponding 3,4-dihydro-o-dithiin isomer, 69, and these authors propose a radical mechanism (page 122) for this process. The structure of 69 was confirmed by elemental and spectroscopic analysis (including a mass spectroscopic fragmentation study) and the formation of dimethyl α-(1,2-diphenylethyl)-succinate (160) on desulphurisation. This unusual rearrangement represents an important and useful method of preparing the inaccessible 3,4 dihydro-o-dithiins in excellent yield.



(70a) (69) (160)

E = CO_2Me

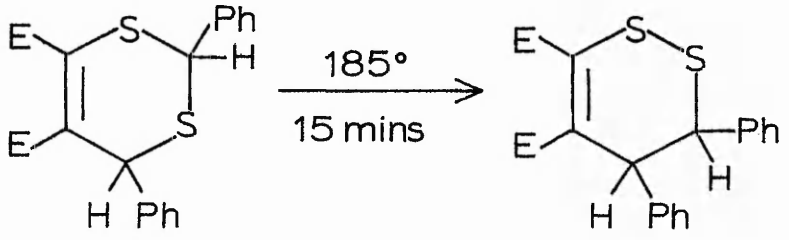
No assignment of configuration at C3 and C4 was made, and none of the reactions of the new 3,4 dihydro-o-dithiin 69 were investigated. This situation has now been remedied by the present study, and a preliminary report of the results has been made[73], notably of the separation and stereochemical assignment of the cis and trans isomers of 69. The results are outlined in Scheme 1, (page 28) and a detailed analysis of the reactions concerning the o-dithiin 69 and similar compounds is presented in the following section.

PART 2. DISCUSSION

1. Preparation of o-Dithiins

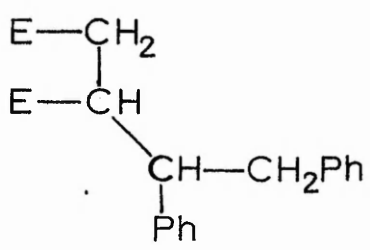
During the pyrolysis of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) at 180-185° under nitrogen, Eisner and Krishnamurthy[71] observed that after 15 minutes the starting material had been transformed cleanly into a new compound. The main changes in the nmr spectrum were the appearance of an AB quartet (centred at δ 4.40 ppm) for the methine protons, and the collapse of the phenyl singlet into a multiplet (δ 7.17 ppm). A yield of 100% was claimed for the reaction, and the product was identified as dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69).

E = CO_2Me



(70a) (69)

The structure of the product cyclic disulphide, 69 was confirmed as that shown above by Raney nickel desulphurisation and characterisation of the resulting diester, 160. Disulphide tests[178] were also carried



(160)

out, and uv and mass spectra were recorded.

The present study deals with the mode of formation, the reactions and the stereochemistry of these unusual dihydro-o-dithiin systems.

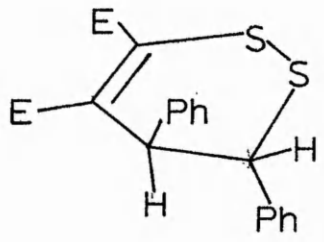
Using the conditions of Eisner and Krishnamurthy[71] for the o-dithiin synthesis, the maximum yield of 69 obtained was 84%. When followed by nmr, the reaction appeared to proceed cleanly and stereospecifically to give a single isomer. However, a close examination of the second and third crops of crystals obtained during work-up of the reaction mixture, revealed that, in addition to the main product (cubes), a second crystalline form (needles) was present. Separation of the two forms was possible because of their differing solubility; the needles (minor product) dissolved much more readily in acetone. The total yield of the minor product was estimated as 3%.

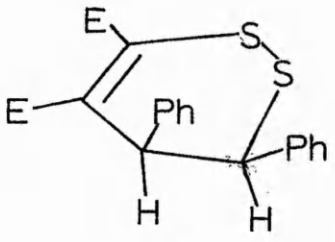
Several experiments were carried out to determine the relationship between the two products. It was thought at first that they were simply polymorphs, but cross-crystallisation failed to interconvert them. The spectroscopic data and melting points for the two compounds were significantly different, although microanalysis showed them both to have the formula $C_{20}H_{18}O_4S_2$. Both gave positive disulphide tests and so it was concluded that they were cis and trans isomers. The spectroscopic data for these o-dithiin isomers are given in Table 5.

TABLE 5.

Dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate

	69 (major)	69a (minor)
ν max, cm^{-1} (KBr)	1742, 1730 (CO_2Me)	1730 (CO_2Me)
" (nujol)	1741, 1730 "	1725 "
" (CCl_4)	1740 "	1740, 1730 "
" (CH_2Cl_2)	1730 "	1730, 1723 "
λ max, nm (MeOH)	223 (ε14800), 269 (ε8000),	223 (ε14800), 270 (ε7700),
	331 (ε2800)	339 (ε3200)
^{1}Hnmr, δ, ppm ($CDCl_3$)	7.21 (m, C_6H_5)	7.1, 6.65 (m, C_6H_5)
(100 MHz)	4.56, 4.41	4.52, 4.44
	(d, H-3, H-4, J=6.0Hz)	(d, H-3, H-4, J=3.6Hz)
	3.88, 3.54 (s, CO_2CH_3)	3.94, 3.56 (s, CO_2CH_3)
^{13}Cnmr, δ, ppm ($CDCl_3$)	139.3 (C-6)	
	138.5 (C-5)	
	54.0 (C-3)	
	48.3 (C-4)	

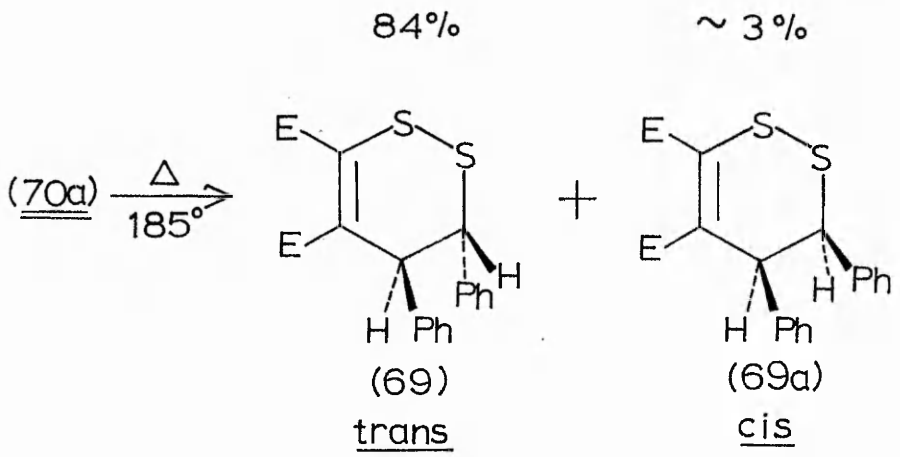




trans (69) cis (69a) E = CO_2Me

Assignment of stereochemistry to the isomers is not possible from the spectroscopic data alone. Since there are constraints imposed on the rotation around the C-3 to C-4 bond by the ring system as a whole, the isomers cannot be considered as simple 1,2 diphenylethanes, and the Karplus equation[179] (which related the dihedral angle between vicinal protons to their coupling constant) cannot be used to assign the stereochemistry.

The salient features in the ^{1}Hnmr spectrum of the minor o-dithiin isomer 69a are firstly, the reduction in the coupling constant for the vicinal methine protons to 3.6 Hz (from 6.0 Hz in the major isomer) and secondly, the appearance of a new broad absorption in the phenyl region at δ 6.65 ppm. This modified coupling of the phenyl groups implies that they are in closer proximity than those in the major isomer. These observations allow a tentative assignment of trans to the major isomer, 69, and cis to the minor, 69a, but clearly, more substantial evidence is required.



Further evidence for this assignment was provided by an examination of the reaction of each of the isomers with trivalent phosphorus compounds, and this is described on page 128.

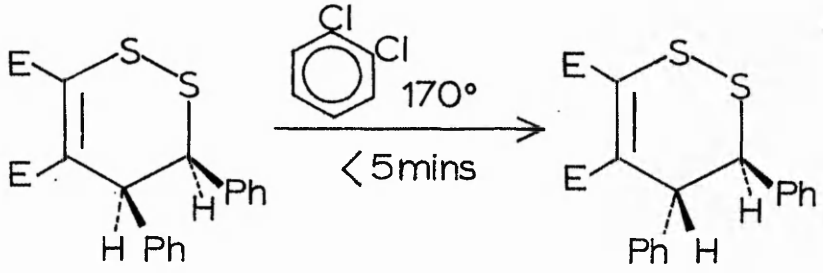
Fortuitously, it was discovered that the thermal rearrangement of m- to o-dithiins could also be carried out in solution. For example, the reaction was found to be complete after 30 minutes' reflux in o-dichlorobenzene, 4 hours' reflux in xylene and about 8 hours' reflux in toluene. These variations allowed considerable flexibility in the reaction; it was found that the shorter the reaction time the better, and so dichlorobenzene was often chosen as the solvent.

Despite initial difficulties, it was found that the solvent was best removed from the product by a two stage process involving firstly, evaporation in vacuo, followed by absorption of the residue onto a silica gel column under suction. Petroleum ether was then used to wash out the last traces of o-dichlorobenzene and the product was recovered by eluting the column with methanol.

When the rearrangement was carried out in a

solvent, (involving a longer reaction time) only the trans isomer was formed; it is possible that this is the product of thermodynamic reaction control, and that the cis isomer is a kinetic product.

Evidence to support this theory was provided when a sample of dimethyl cis-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69a) was heated in o-dichlorobenzene in the probe of the nmr spectrometer. When the temperature reached 170°, the AB quartet attributed to the methine protons collapsed, and within a few minutes, a new quartet, identical to that of the trans isomer, 69, had appeared. The same result was obtained after heating the cis isomer in xylene under reflux for 4 hours or in toluene for 8 hours. Thus, it is not surprising that none of the minor isomer was obtained after 30 minutes reflux in o-dichlorobenzene.

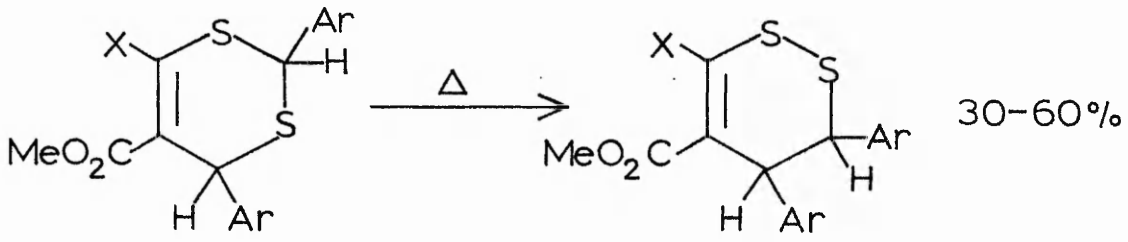


cis (69a) trans (69)

The same isomerisation cannot be brought about by treatment with organic bases such as DABCO or triethylamine; decomposition of the disulphide ring occurred on treatment with these reagents.

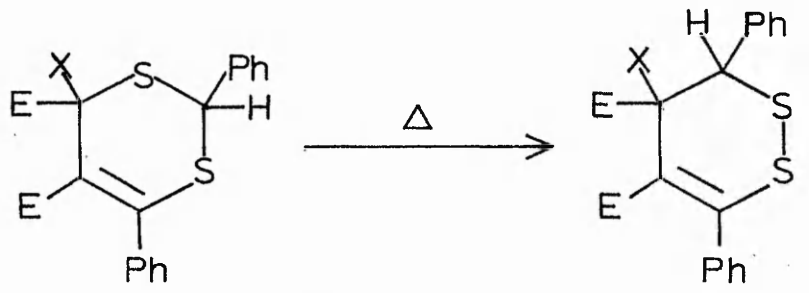
Using one of the methods just described, the

o-dithiin analogues 69b-d were isolated by the thermal rearrangement of the corresponding m-dithiins. The p-anisyl derivative 69e could not be isolated in a crystalline form although the ^{1}Hnmr spectrum showed that it had been formed. The yields were typically around 50%, paralleling those for the corresponding syntheses of m-dithiin analogues (and again significantly lower than the yields in the phenyl series). For the analogues 69b-e, only one stereoisomer was observed; this is presumably the trans, since there was good agreement between the J values for these analogues and that in the phenyl trans isomer, 69.



(70) b. X = H, Ar = Ph (69)
c. X = CO_2Me, Ar = p-Cl.C_6H_4
d. X = CO_2Me, Ar = p-Me.C_6H_4
e. X = CO_2Me, Ar = p-MeO.C_6H_4

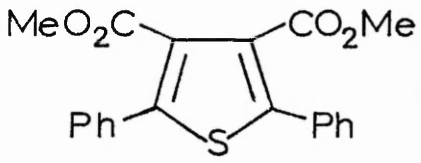
The thermal rearrangement of m- to o-dithiins also proved to be successful for m-dithiin tautomers such as dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a) and its C-6 deutero-analogue (76b). These were rearranged to their respective o-dithiins, 161a and b:



(76) (161)

a. X = H
b. X = D
c. X = Me E = CO_2Me

The above reaction did not, however, proceed as smoothly as those in the 4H-tautomeric series; yields were approximately 40%, and the product was frequently difficult to crystallise. In addition, a byproduct was isolated; it was identified as dimethyl 2,5-diphenyl-thiophen-3,4-dicarboxylate (97). This suggests that



(97)

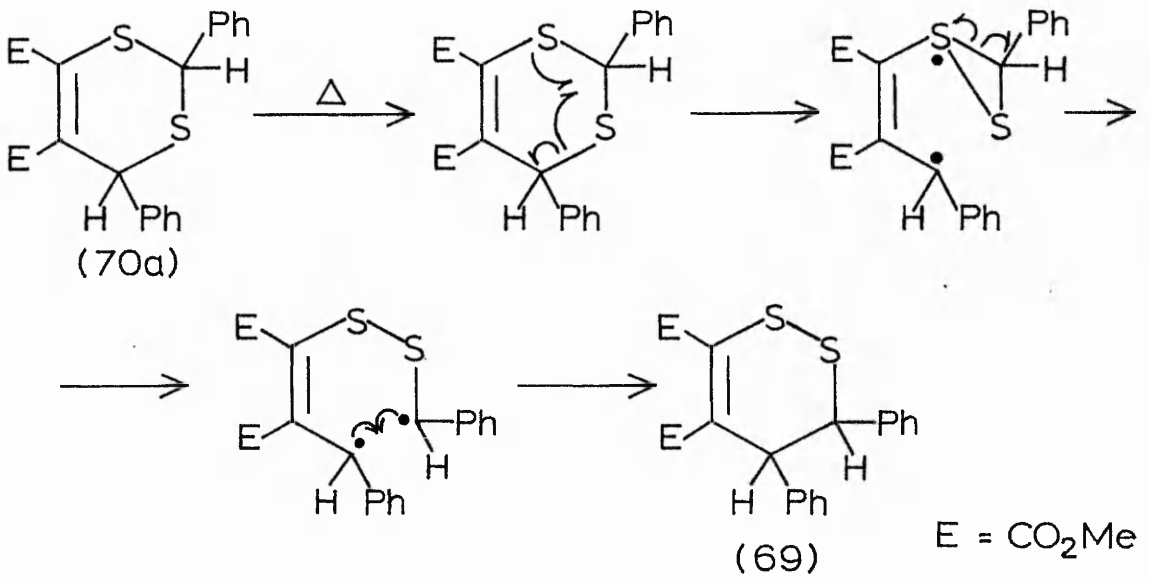
the o-dithiins derived from the 6H-tautomeric series are thermally less stable than their 4H-counterparts and lose hydrogen sulphide on heating to give the corresponding thiophen.

The C-6 methyl-substituted m-dithiin, 76c, could not be thermally rearranged to the corresponding o-dithiin 161c. Complex mixtures were obtained on refluxing 76c in o-dichlorobenzene, and when controlled experiments were carried out at several different

temperatures, it was found that below 160° no reaction at all occurred, whereas above 170° decomposition took place. Unlike its 6H-counterpart, o-dithiin 161c cannot achieve stability (by loss of hydrogen sulphide) by forming a thiophen derivative, hence, decomposition occurs.

Having examined the scope of the thermal rearrangement, it is now appropriate to examine the mechanism by which it takes place.

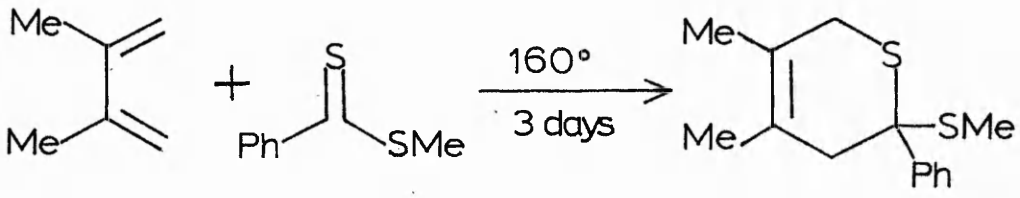
Eisner and Krishnamurthy[71] suggested, without evidence, the following radical mechanism to explain the course of the reaction:



In order to assess the possibility that this mechanism is correct, several experiments were conducted. It was found that the inclusion of free-radical scavengers (e.g. p-benzoquinone or 2,2-diphenyl-1-picrylhydrazyl, DPPH) did not affect the outcome of the reaction; nor was there significant change when radical initiators were

introduced. It seems very likely, therefore, that some other mechanism is operating.

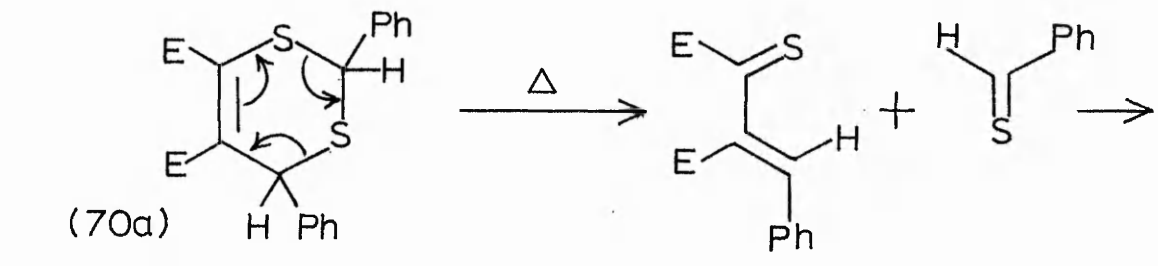
An alternative mechanism is a retro Diels-Alder reaction. Several examples of the involvement of the thiocarbonyl function in Diels-Alder cycloadditions are known; the following reaction is a recent example[180] of such a case:



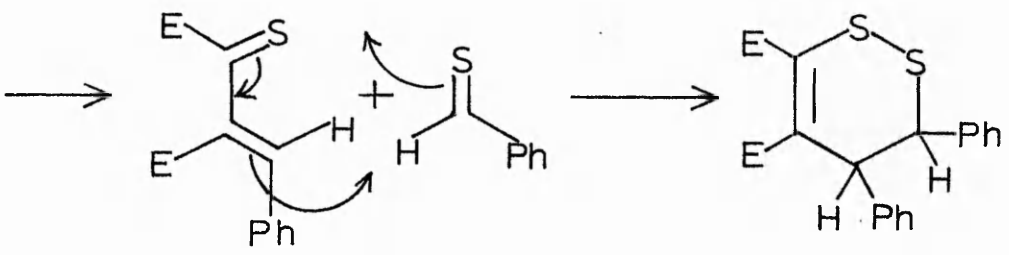
70%

The path of the retro Diels-Alder reaction in the present case would thus be:

E = CO_2Me

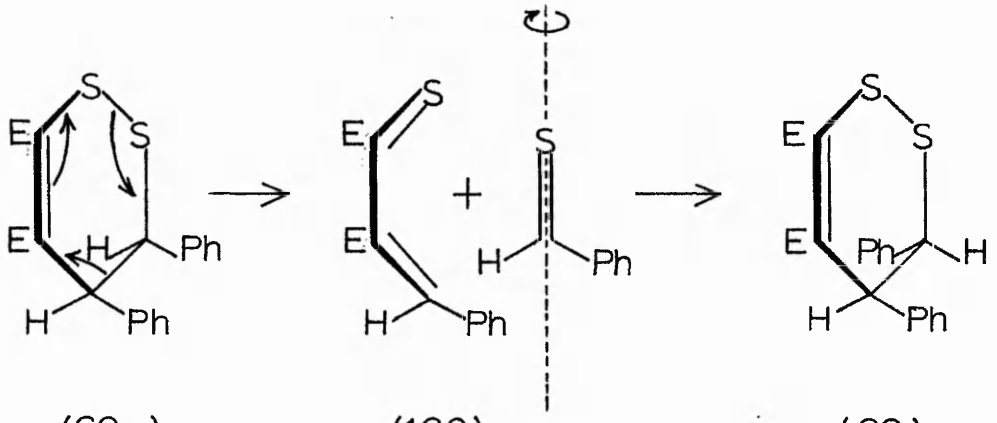


(70a)



(69)

The first indications that this mechanism may operate are to be found in the mass spectra of both starting material and product, which indicate initial loss of the thiobenzaldehyde fragment by a retro Diels-Alder pathway[86] (see page 26). Once thiobenzaldehyde (which is extremely reactive) is produced, it prefers to recombine in a 'sulphur atom to sulphur atom' fashion, presumably because of the greater efficiency of orbital overlap for this mode of union. The fact that o-dithiins fragment in a similar way might explain the isomerisation of the cis to the trans isomer which occurs rapidly at temperatures above 170° (page 119).



(69a) (162) (69)

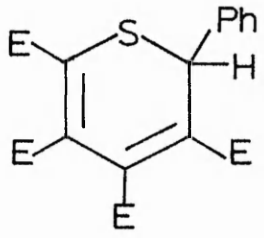
cis trans

In order to substantiate these theories, the ideal target is obviously to trap the diene intermediate, (162) shown above. The m-dithiin 70a was chosen as a potential diene source in these experiments (rather than the cis o-dithiin isomer, 69a) because the reaction in this case takes a reasonable period of time (20-30 mins)

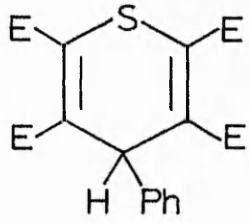
and the chances of trapping the diene are thus maximised.

The introduction of an alternative dienophile which can compete with thiobenzaldehyde, should, in theory, give an alternative Diels-Alder adduct. First maleic anhydride, then methyl propiolate was included in the reaction but no new Diels-Alder adducts were obtained. When dimethyl acetylenedicarboxylate (DMAD) was included, however, other components were formed. These were isolated by chromatography and were identified by nmr and mass spectroscopy as the novel 2H- and 4H-thiopyrans, 163 and 164, shown below:

E = CO_2Me

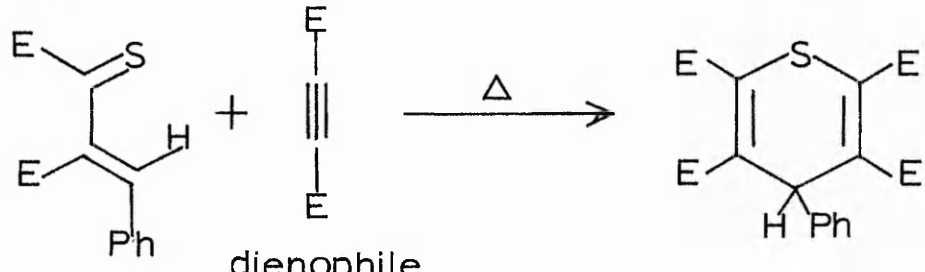


(163)



(164)

The 2H-thiopyran 163 may simply be the addition product of thiobenzaldehyde to DMAD, and since thiobenzaldehyde could conceivably have been formed via some other mechanism, no conclusion can be drawn. The isolation, on the other hand, of the 4H-thiopyran, 164, provides convincing evidence that the retro Diels-Alder mechanism (page123) operates in the rearrangement of m- to o-dithiins.

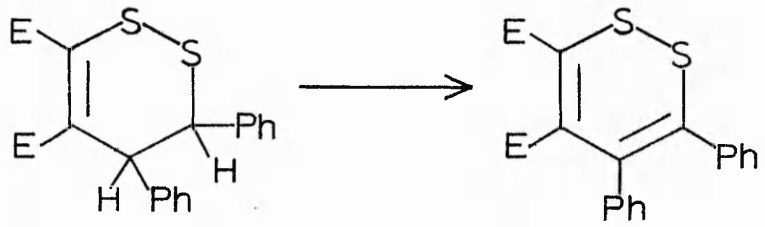


(162) dienophile (164)

2. Reactions of o-Dithiins

A. Dehydrogenation

In view of the rarity of monocyclic anhydro-o-dithiins, attempts were made to dehydrogenate one of the dihydro-o-dithiin systems.



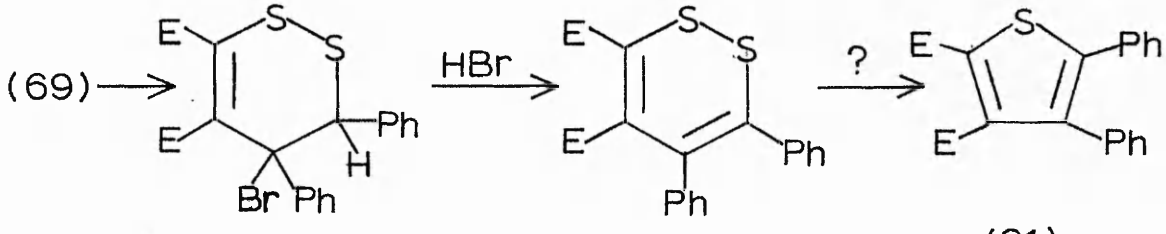
(69) (165)

The trans o-dithiin, 69, because it is readily available, was used in these experiments, but in retrospect, the cis isomer, 69a, might have been more likely to undergo dehydrogenation, due firstly to ease of access by the reagent, and secondly to the higher ground state energy of the starting material.

The high-potential quinones o-chloranil and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were employed for this purpose, but neither of them had any effect on the o-dithiin, 69, even after prolonged heating under reflux in xylene. Further attempts were made to abstract a hydride ion using trityl fluoroborate[181], but this gave no reaction at lower temperatures and caused decomposition of the dithiin above 100°. These efforts were arguably unlikely to succeed because it seems certain that the anhydro-o-dithiin, 165, if formed, could not withstand the vigorous conditions necessary to bring about

the reaction.

In an effort to circumvent this problem, attempts were made to replace one of the methine protons by bromine, with the aim of eliminating hydrogen bromide to give the desired anhydro-o-dithiin, 165. N-Bromosuccinimide is well known[182] to brominate allylic positions (frequently with spontaneous dehydrobromination giving a diene system) and so this method was employed.



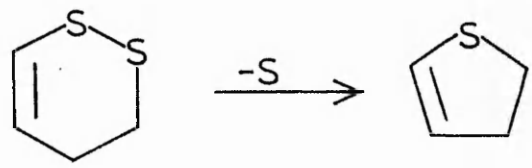
(165) (91)

The bulk (75%) of the starting material was recovered, but, further, some dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91) was isolated. Since it was necessary to carry the reaction out at 60°, it is extremely likely that bromination/dehydrobromination had occurred to give the anhydro-o-dithiin, 165, which then spontaneously lost elemental sulphur (in a manner common to such systems; for examples, see introduction) to give the observed thiophen (91). The same result was obtained despite several variations in conditions; no reaction at all took place below 60°.

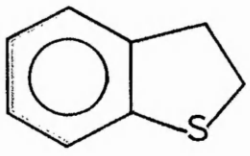
B. Desulphurisation

As disulphides, o-dithiins can be involved in many different types of reaction, most of which involve irreversible disulphide bond cleavage and hence ring opening, putting them largely beyond the scope of this study.

The selective removal of one of the sulphur atoms in the o-dithiin systems, however is of great interest because it leads to a 2,3-dihydrothiophen (2-thiolene).



2,3-Dihydrothiophens, although stable molecules having essentially a planar structure, are particularly rare, because it is virtually impossible to form them by selective hydrogenation of one of the double bonds in thiophens. Thus, nearly all of the 2,3-dihydrothiophens known have been made by some kind of independent cyclisation[183] or ring contraction. Further, most of these are either fused benzodihydrothiophens (166), or 3,4-dihydrothiophens (3-thiolenes) (167).



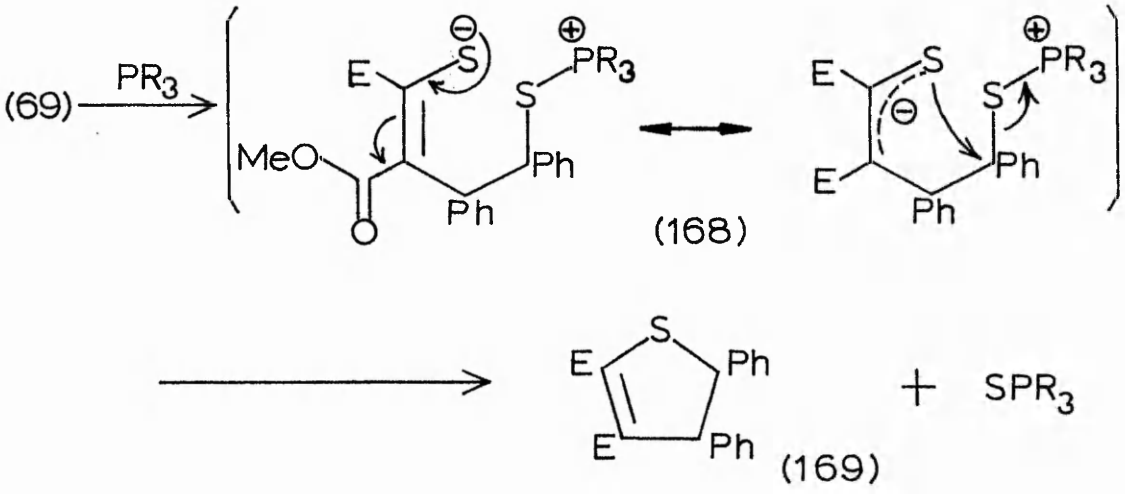
(166)

(167)

The desulphurisation of o-dithiins is therefore a potentially important route to these inaccessible systems.

The desulphurisation of disulphides is normally carried out using a trivalent phosphorus moiety[184]. The reactions of these compounds have been extensively reviewed[185], and the three main types of compound which will effect the conversion are tertiary phosphines (e.g. Ph_3P), tertiary phospites (e.g. $(MeO)_3P$) and triaminophosphines[186] (e.g. $(Me_2N)_3P$, hexamethylphosphorus triamide).

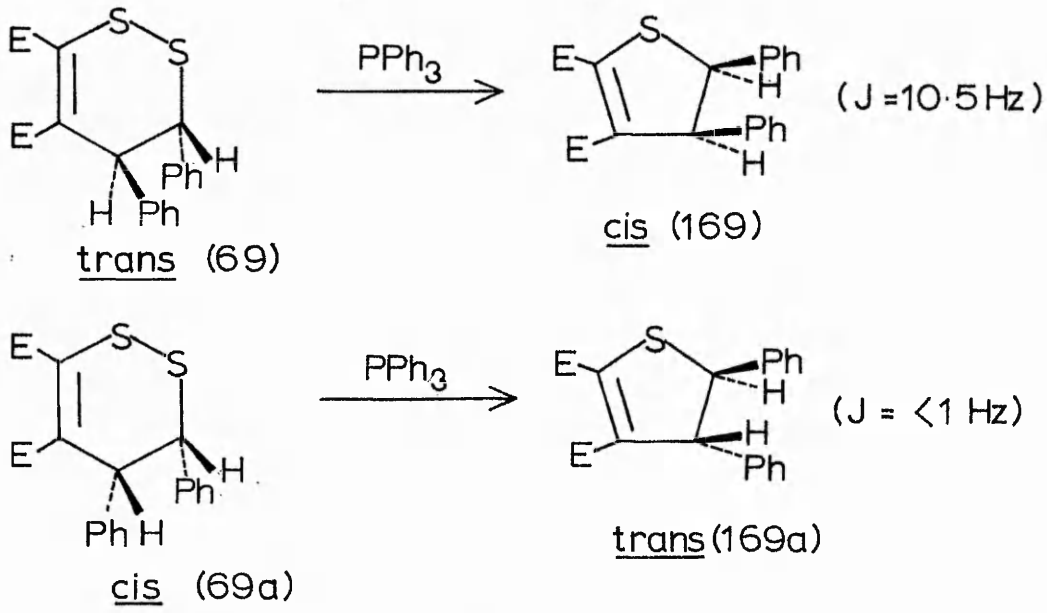
The driving force in the reaction is probably the polarisability of phosphorus and its great affinity for sulphur. The mechanism is believed to be ionic in nature, the phosphorus attacking the sulphur atom which can least stabilise a developing negative charge. In this respect, the reaction is controlled to a certain degree by the efficiency as a leaving group of the sulphur atom which is not under direct attack from the phosphorus compound.



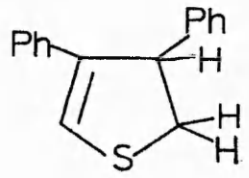
The leaving group, 168, in this reaction (a thiolate ion) is stabilised by conjugation through the double bond as shown. Notably, the recyclisation, in which S-1 attacks C-3 in an S_N2 fashion, proceeds with inversion of configuration at C-3. This is a characteristic of phosphine or phospite desulphurisations and the reaction has been reported[186] to be entirely stereospecific in the case of triaminophosphines. Considerable mechanistic work has now been carried out on these reactions[187,188], mainly because of the applications to natural products, many of which contain disulphide linkages.

The cis and trans forms of dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69a and 69) were both treated with triphenylphosphine at room temperature, and were found to react cleanly and completely over a period of several hours to give the trans and cis isomers of dimethyl 2,3-dihydro-2,3-diphenylthiophen-4,5 dicarboxylate (169a and 169) respectively, in quantitative yield.

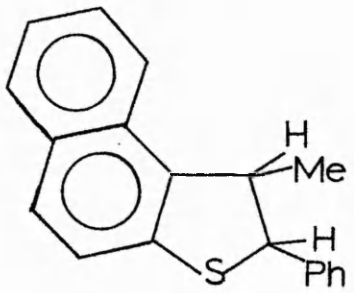
Unfortunately, the byproduct, triphenylphosphine sulphide, could not be removed by standard work-up procedures, and it was necessary to purify by chromatography.



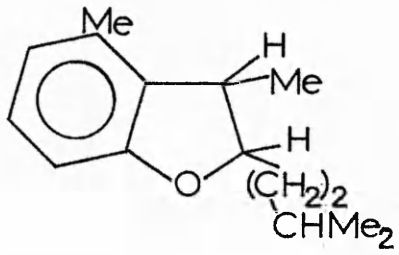
All the spectroscopic data for the products were in agreement with the above structures; central to these assignments were the coupling constants observed for the methine protons in the 2,3-dihydrothiophens. The few comparable compounds mentioned in the literature have coupling constants of the same order, with the cis



J_{cis} = 9.6 Hz
J_{trans} = 3.6 Hz
Ref. 189



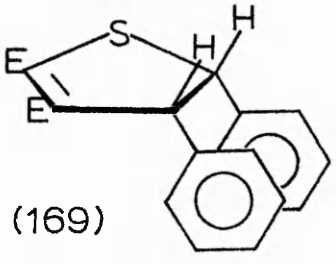
J_{cis} = 7.0 Hz
J_{trans} = 1.5 Hz
Ref. 183



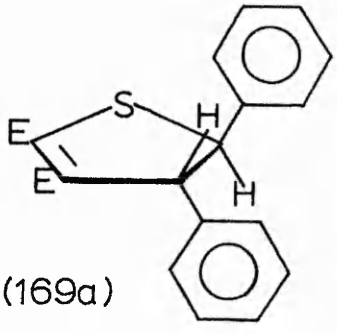
J_{cis} = 7.0 Hz
J_{trans} = 4.8 Hz
Ref. 190

coupling constant always greater than the trans. This in turn, provides more evidence that the assignments given to the starting materials are correct.

Identical inversions of configuration were obtained when the cis and trans o-dithiins 69a and 69 were treated with hexamethylphosphorus triamide, giving the trans and cis dihydrothiophens 169a and 169 respectively.



(169)

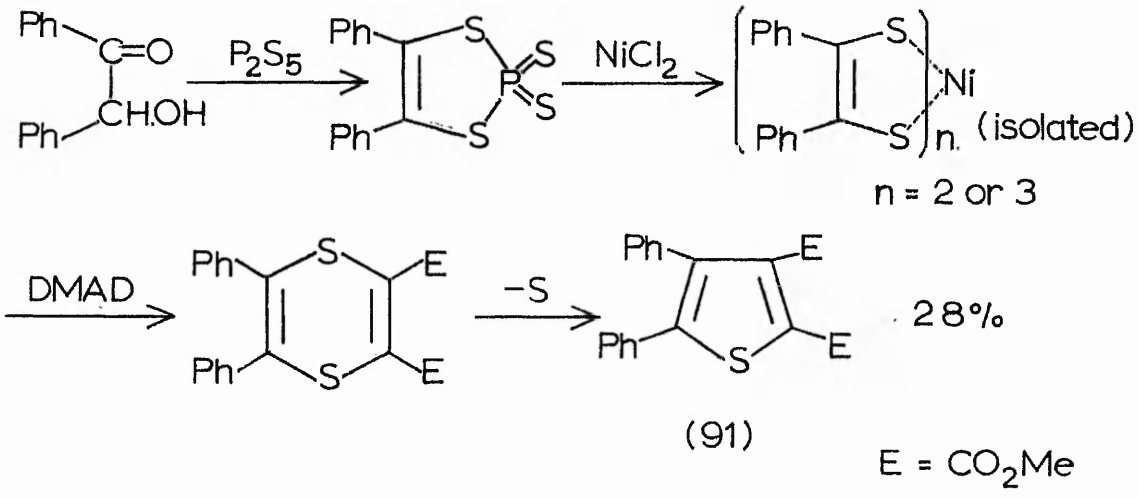


(169a)

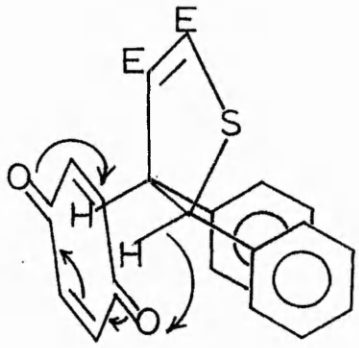
It was deduced that dehydrogenation of 169 and 169a should proceed readily to give dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91). The 2,3-dihydrothiophen system, however, is almost planar, and this means that the phenyl groups in the cis isomer (169) are eclipsed, imparting considerable strain to the ring. It was expected, therefore, that some variation in rate would be observed when the cis and trans isomers were reacted with a dehydrogenating agent such as DDQ or o-chloranil.

This was indeed found to be the case. The 2,3-dihydrothiophen, 169, to which the cis configuration had been assigned, was dehydrogenated in high yield by DDQ at room temperature after 1 hour. In stark contrast,

it was found (by making the conditions progressively harsher) that 12 hours' reflux in chlorobenzene ($\sim 170^{o}$) with an excess of DDQ , was required to dehydrogenate the trans isomer, 169a. Detection of the dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91) was facilitated by its strong fluorescent uv absorption, and for the purposed of comparison, a pure sample was prepared independently using the method of Schrauzer and Mayweg[133]:

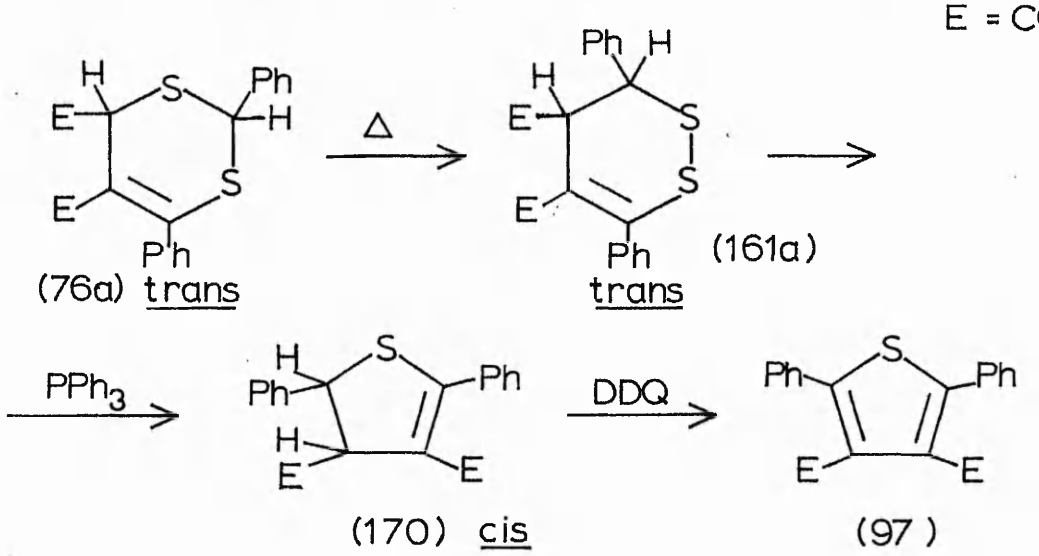


Dehydrogenation using high potential quinones such as DDQ is known[191] to proceed with the removal of a hydride ion, followed by proton loss. For the cis 2,3-dihydrothiophen isomer, 169, this process may be aided by the operation of a cyclic mechanism, as shown below.



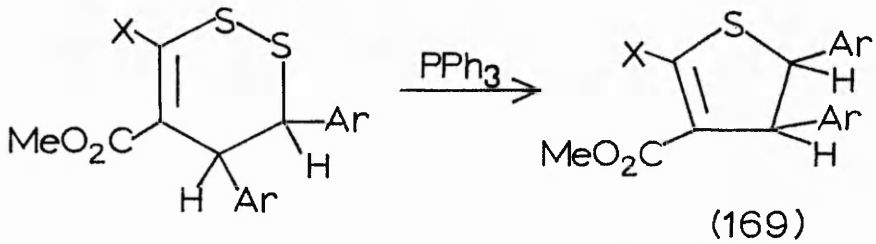
The close proximity approach of the reagent in this scheme is clearly not possible for the trans isomer, 169a, because of the presence of the bulky phenyl ring. This, together with the fact that the cis isomer will already have a higher ground state energy than the trans, rationalises the sharply contrasting reactivity observed between the two, providing further supportive evidence for the assignments made in the series as a whole.

Dimethyl 3,4-dihydro-3,6-diphenyl-o-dithiin-4,5-dicarboxylate (161a) formed by thermal rearrangement of the 6H-m-dithiin tautomer, 76a, underwent quantitative desulphurisation when treated with triphenylphosphine. The product, dimethyl 2,3-dihydro-2,5-diphenylthiophen-3,4-dicarboxylate (170), reacted readily at room temperature with DDQ to give dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97, confirmed by comparison of spectroscopic data with literature[193] values). The stereochemistry for this sequence (by analogy with the normal series just described) is assumed to be as follows:



(76a) trans (161a) trans (170) cis (97)

The same desulphurisation was observed for the p-chlorophenyl analogue in the normal (m-dithiin 4H-tautomeric) series.



(69) (169)

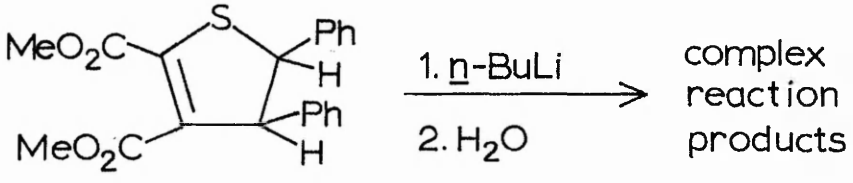
b. X = H, Ar = Ph

c. X = CO_2Me, Ar = p-ClC_6H_4

When the monoester, 69b, was treated with triphenylphosphine under the usual conditions, little or no reaction occurred. It was found instead, that several hours' reflux in ethanol with an excess of triphenylphosphine was required to form the desired 2,3-dihydrothiophen, 169b. This observation may be accounted for in terms of the leaving group ability of the sulphur atom attached to the vinyl group. When there is no electron-withdrawing substituent at C-6, the stabilisation of the developing negative charge at S-1 is reduced, and the reaction is retarded relative to

the diester (69a). It is a little surprising that this effect should be so marked, since the stabilisation of the incipient thiolate intermediate is largely mesomeric and thus directed through the ester group at C-5.

In the light of the finding (page 44) that m-dithiins such as 70a can be tautomerised when treated with strong bases such as n-butyllithium, followed by water, a parallel reaction may be postulated for 2,3-dihydrothiophens. Accordingly, dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169) was treated with n-butyllithium using standard conditions for proton abstraction. In the event, it was found that several components were formed (none of which corresponded to the desired tautomer) and unchanged starting material predominated; no improvement was observed when DABCO

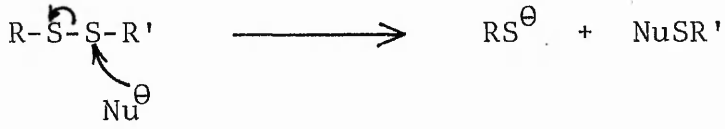


(169)

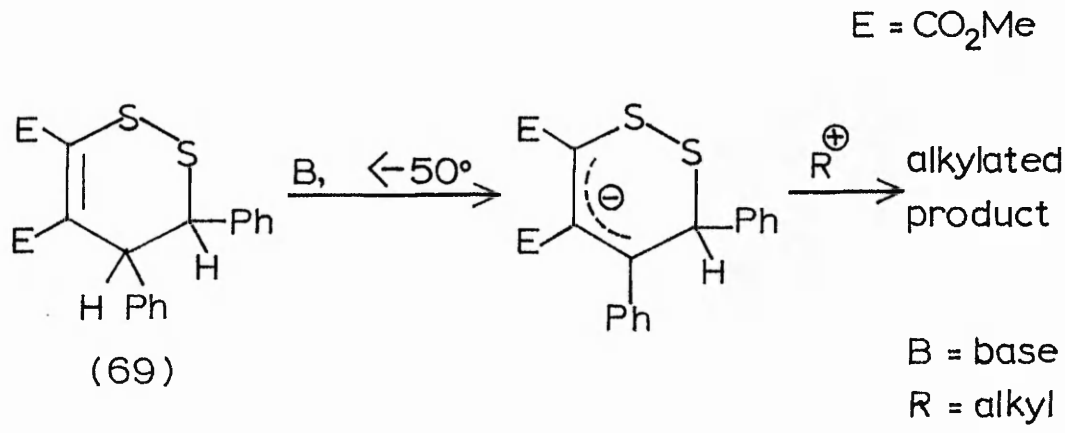
was included in the reaction.

C. Treatment with Base

In view of the relative ease with which disulphide bonds are cleaved by nucleophiles[162-164], it was expected that treatment of the o-dithiins with reagents such as sodium hydroxide or sodium borohydride should cause ring opening to occur.



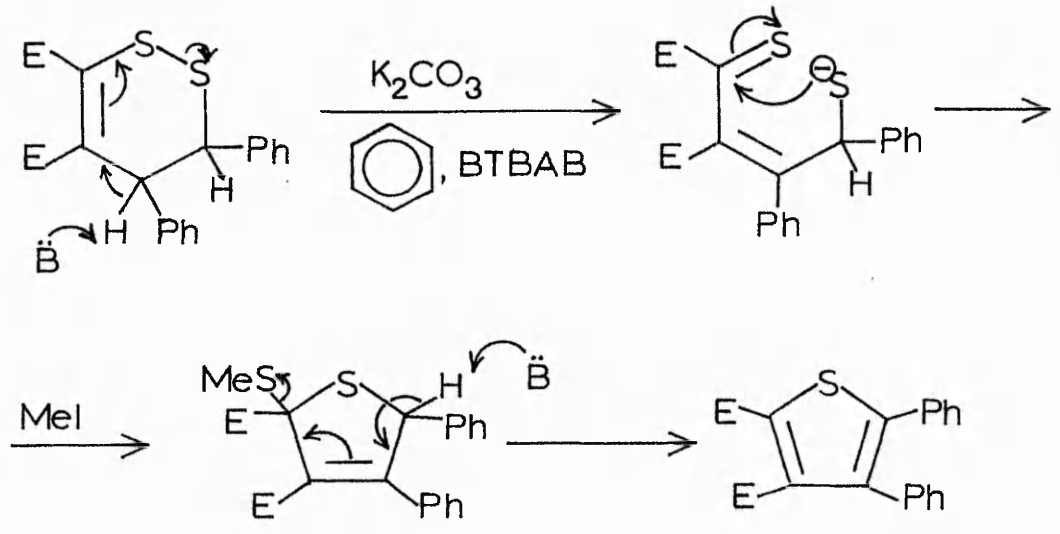
This was indeed found to be the case, (see the section on hydrolysis, page148), but strong bases such as n-butyllithium and lithium diisopropylamide were found to cleave the disulphide bridge much less readily when the reaction was carried out below -50°. In each case, nmr analysis of the crude reaction product showed that some ring opening and S-alkylation had occurred, but that much of the starting material remained. These results raised hopes that at sufficiently low temperatures, specific proton abstraction and subsequent alkylation (similar to that observed in the m-dithiin series) might be observed, i.e.



If alkyllithiums such as n-butyllithium are used in conjunction with a tertiary amine such as diazabicylo [2.2.2] octane (DABCO) or N,N,N',N'-tetramethylethylenediamine (TMEDA), the properties of the alkylithium are modified[97]. As a result of complexation with the tertiary amine, the charge separation in the alkylithium is increased, thus increasing its basicity at the expense of its nucleophilicity. It was therefore hoped that such a modification would decrease the chances of disulphide bond scission when o-dithiins were treated in this way.

Accordingly, o-dithiin 69 was treated with n-butyllithium and DABCO below -50° then with deuterium oxide. No deuteration was observed, and mainly unreacted starting material was isolated. When the reaction was repeated at higher temperatures, the proportion of unreacted starting material decreased but no deuteration had taken place.

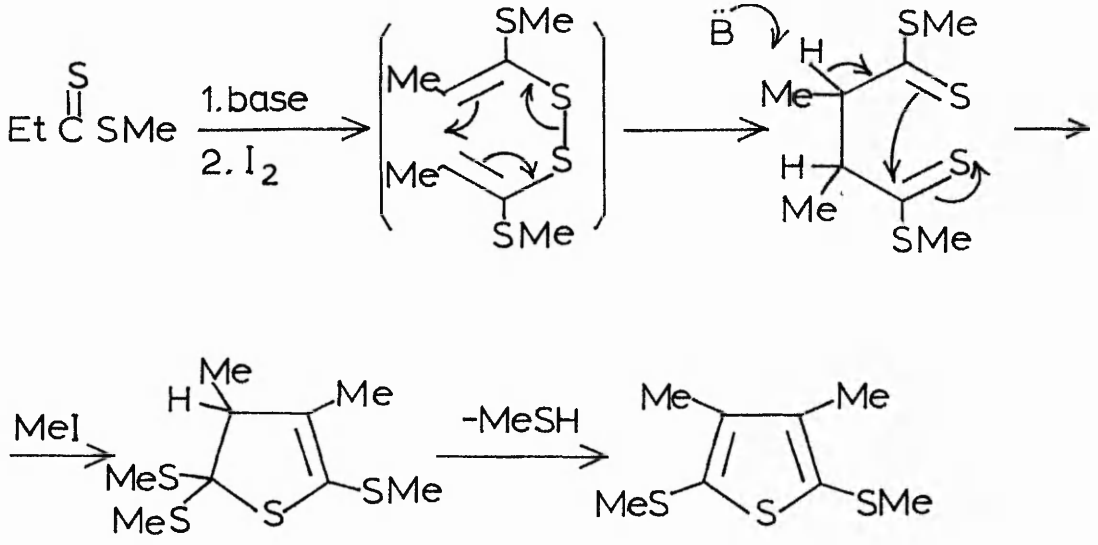
Having failed to abstract a proton using this method, it was decided to try the other approach which had been successful for m-dithiins, namely, potassium carbonate in the presence of a phase-transfer catalyst. Using benzyltri-n-butylammonium bromide (BTBAB) as catalyst in refluxing benzene, a mixture was formed. However, when methyl iodide was included, dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91)was formed, presumably by a mechanism which parallels the base catalysed transformation of m-dithiins to symmetrical thiophens described on page 78.



(91)

E = CO_2Me

Other products were formed, but they could not be identified; it is likely that some of these arose from direct disulphide cleavage. The mechanism proposed above for thiophen formation is similar to that postulated by Larssen et al[199] for the base catalysed cylisation of methyl dithiopropionate.



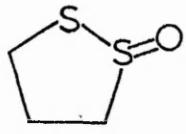
D. Oxidation

Since the characterisation of allyl 2-propene-1-thiolsulphinate (171, allicin) as the active anti-bacterial agent contained in common garlic, considerable interest has been centred on the structure, chemistry and properties of thiolsulphinates; RS(O)SR.

$$CH_2 = CHCH_2 - \underset{\underset{O}{\|}}{S}-SCH_2CH = CH_2$$

(171)

Alkyl thiolsulphinates have been found to possess tumour-inhibiting, antifungal and antiviral activity[200], and certain cyclic thiolsulphinates related to 1,2-dithiolane 1-oxide have been found to occur naturally and to exhibit biological activity[37,198].

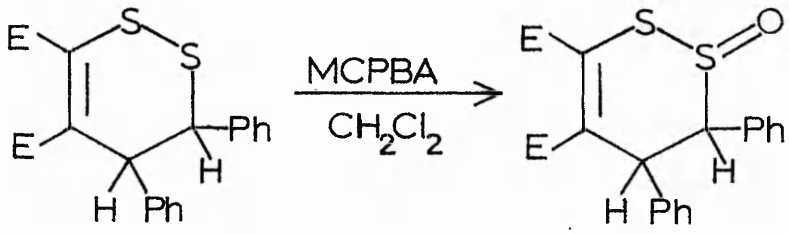


The synthesis therefore, of o-dithiin mono-sulphoxides is of particular interest in the light of the reported reactivity and low stability of many molecules possessing the S(O)-S linkage[200].

Several of the reagents and conditions used for the oxidation of m-dithiins (see Table 2, page 60 for a summary of the results) were applied to o-dithiins; again, the best oxidant was found to be m-chloroperbenzoic acid (MCPBA). The reaction between dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (cis, 69a or trans,

69) and MCPBA was quite rapid (~1 hour), and resulted in the formation of the cis and trans monosulphoxides, 172a and 172 , respectively. In each case, a single sulphoxide isomer was isolated, the alternative product being formed in trace amounts at most.

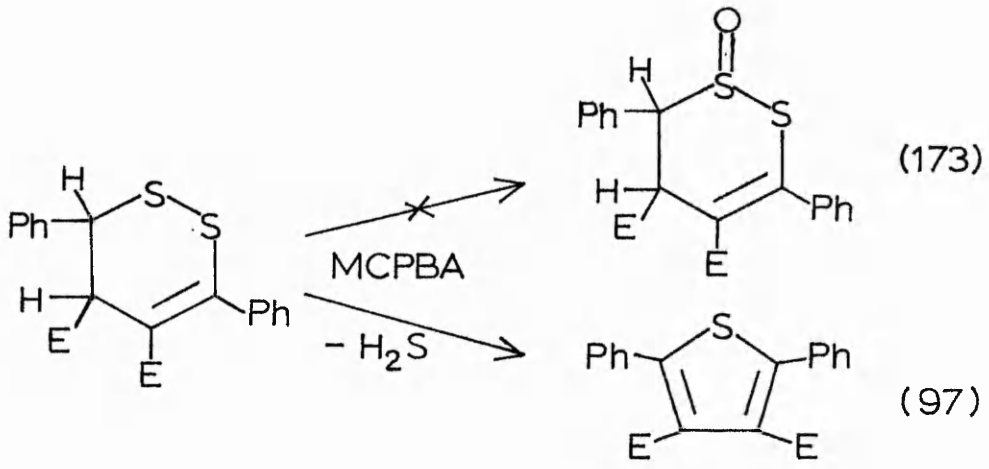
$E = CO_2Me$



trans or cis (69 or 69a) → (172 or 172a)

^{13}CNmr studies carried out on the sulphoxide (172) obtained from the trans o-dithiin isomer confirm that it is the sulphur atom in position 2 which is oxidised; on oxidation, the C-3 (α) proton is greatly deshielded and the C-4 (β) proton is slightly shielded. These are the α and β effects expected on sulphoxide formation[125].

When the o-dithiin 161a, derived from the (tautomeric) 6H-m-dithiin series, was treated with MCPBA, no sulphoxide was isolated. Instead, the resulting mixture gave dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97) in approximately 50% yield.

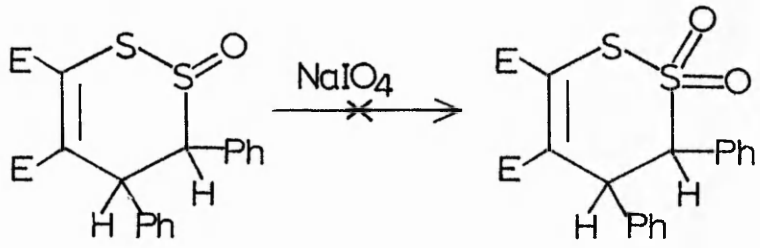


(173)

(97)

The sulphoxide 173 may have been formed as a minor product; the limited availability of the starting material precluded further work on this reaction and so it is not known whether the thiophen, 97, was a direct product of the reaction of the o-dithiin, 161a, or simply a decomposition product of the sulphoxide, 173.

Having successfully formed the cis and trans isomers of 5,6-dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide, the properties of the trans isomer, 172, which was available in larger quantity were investigated further.



(172)

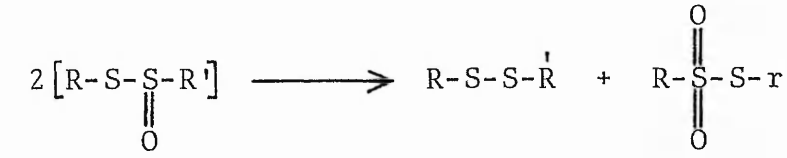
$E = CO_2Me$

Oxidation of cyclic thiolsulphinates to thiolsulphonates has been achieved using potassium metaperiodate in aqueous isopropanol[205] with iodine as a catalyst. This reaction is also reported to proceed

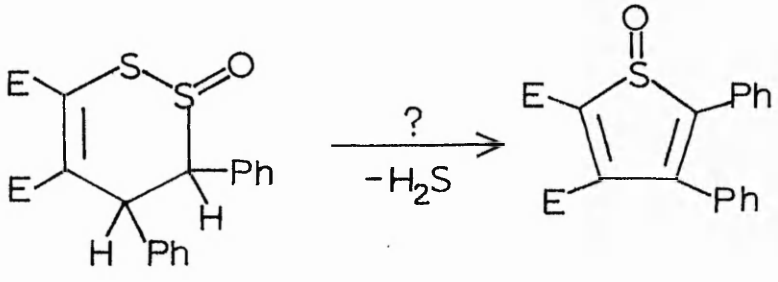
in aqueous dioxan, acetonitrile or acetic acid[206]. When applied to the o-dithiin monosulphoxide, 172, no reaction was observed.

Kice and co-workers[162-164] have prepared almost all of the combinations of S-oxides and -dioxides of dibenzo [c,e]-o-dithiin using standard reagents. In the present work however, reaction of o-dithiin monosulphoxide, 172 with MCPBA gave a multicomponent mixture which contained no new components which were more polar than the starting material (as would have been expected, had sulphone formation occurred).

Certain thiolsulphinates are known to spontaneously disproportionate to the corresponding disulphides and thiolsulphonates[200].



No evidence of a similar disproportionation was found for the o-dithiin sulphoxides, but it was noted, however, that some decomposition occurred during storage. The o-dithiin monosulphoxide, 172, appeared to give off hydrogen sulphide gas which was detected by lead acetate paper (as well as by smell).

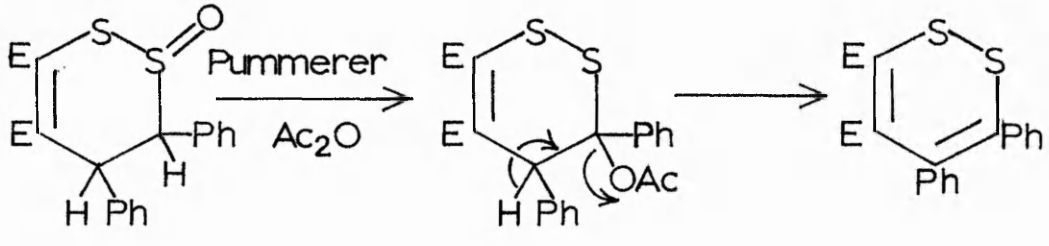


(172)

Analysis of the sample (nmr, tlc) however, did not show the appearance of any new components, and so it was assumed that the degradation was extremely slow. In an attempt to speed up the reaction, the compound was heated to a temperature just below its melting point, but the evolution of hydrogen sulphide was not observed. Pyrolysis at above the melting point resulted in the formation of a complex mixture within a few minutes.

Treatment of 172 with n-butyllithium at -78° produced a mixture consisting entirely of ring opened material, as evidenced by nmr spectroscopy.

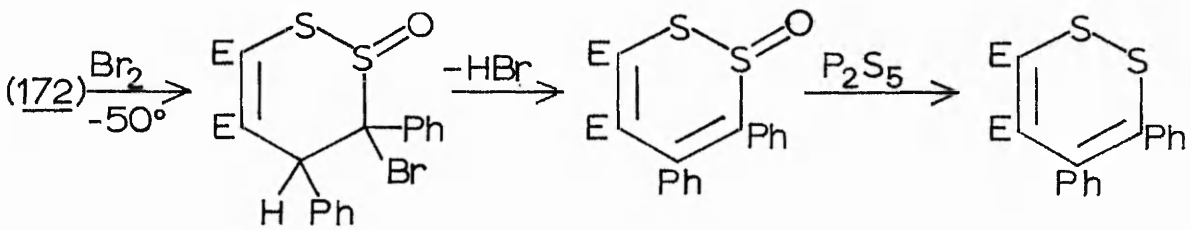
When the o-dithiin monosulphoxide, 172, was heated under reflux in acetic anhydride, a reaction took place over a period of several hours. The resulting mixture, unfortunately, could not be purified by chromatography and so the involvement of a Pummerer rearrangement can neither be confirmed nor ruled out. The probable product (174) of such a reaction might be expected to undergo concomitant elimination to the (presumably) unstable anhydro-o-dithiin 165.



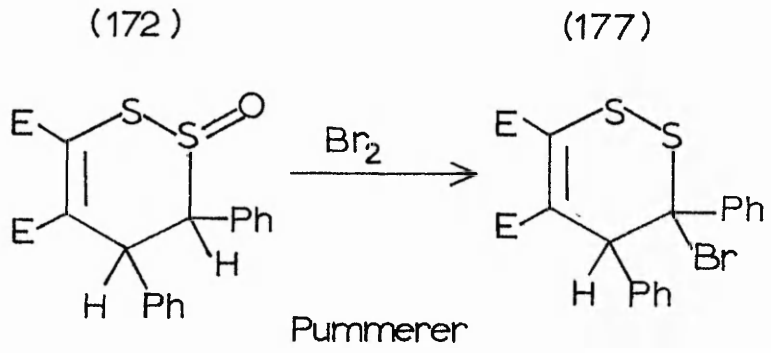
(172) (174) (165)

Since this reaction is carried out in refluxing acetic anhydride, it is hardly likely that the product anhydro-o-dithiin, 165, would survive. The following scheme, however, utilises relatively mild conditions whilst operating on the same principle of elimination to give the anhydro-o-dithiin.

$E = CO_2Me$



It has been shown frequently that sulphoxides can be α-halogenated by bromine and pyridine[201], iodobenzene dichloride and pyridine[202], sulphuryl chloride[203], and by several other reagents[204]. The presence of a base such as pyridine serves to suppress the Pummerer-type rearrangement (which would produce the α-halogeno sulphide, 177) by reacting with the hydrogen halide formed in the reaction.

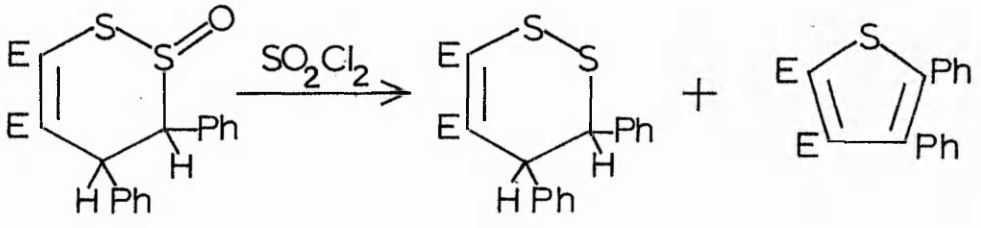


It was considered that the formation of the α-bromo sulphoxide, 176, was more likely to succeed than a Pummerer reaction, since the anhydro-o-dithiin sulphoxide, 175, (formed by dehydrohalogenation of the α-halogeno sulphoxide) is partially stabilised by the electron withdrawing effect of the sulphoxide oxygen.

Treatment of the o-dithiin sulphoxide 172 with bromine in the presence of pyridine and silver nitrate using the conditions of Cinquini[201] resulted in the formation of a mixture. The main component was isolated in very low yield, and although nmr spectroscopic analysis showed that the proton α to the sulphoxide had been removed, mass spectroscopic analysis indicated that no bromine had been incorporated in the product. When the reaction was conducted in the absence of pyridine, an intractable mixture was obtained.

Reaction of the same sulphoxide with sulphuryl chloride gave a three component mixture, from which the two main components were isolated; these were characterised as dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69) and dimethyl 2,3-diphenyl-thiophen-4,5-dicarboxylate (91). No chlorinated species was detected.

$E = CO_2Me$

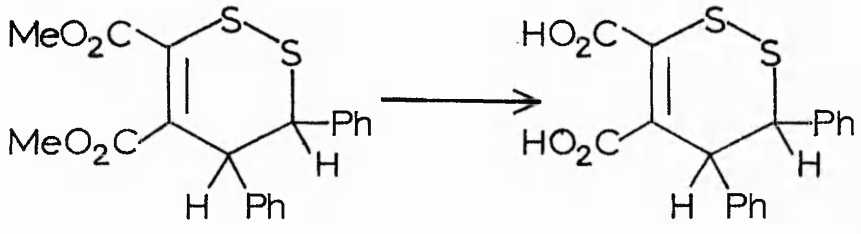


(172) (69) (91)

In general then, it was found that (in common with most thiolsulphinates) the o-dithiin monosulphoxide, 172, was too labile to allow clean reaction with a large number of reagents.

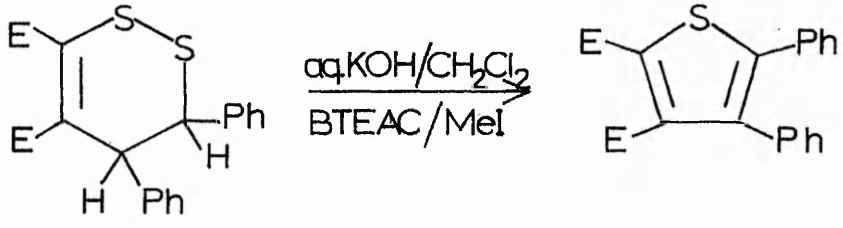
E. Hydrolysis

For similar reasons to those given in the discussion on m-dithiin hydrolysis (page 76) it was decided to attempt the same cleavage in the o-dithiin series. Considering the lability of the disulphide bond, together with the many failures of direct hydrolysis experienced with the m-dithiins, success in the reaction depicted below did not seem likely.



(69) (178)

As expected, treatment of the o-dithiin diester, 69, with hydroxide ion in a homogeneous reaction brought about ring decomposition to multi-component mixtures. When treated with hydroxide ion in a two phase system, however, using a phase-transfer catalyst, an identical reaction occurred to that given by potassium carbonate (page 138). The mechanism for this transformation is almost certainly analogous to that predicted for the same reaction in the m-dithiin series, and this is given on page 78 . The product, dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91), was obtained in 21% yield; the other reaction products were similar to those obtained by homogeneous hydroxide treatment (thin-layer chromatography).

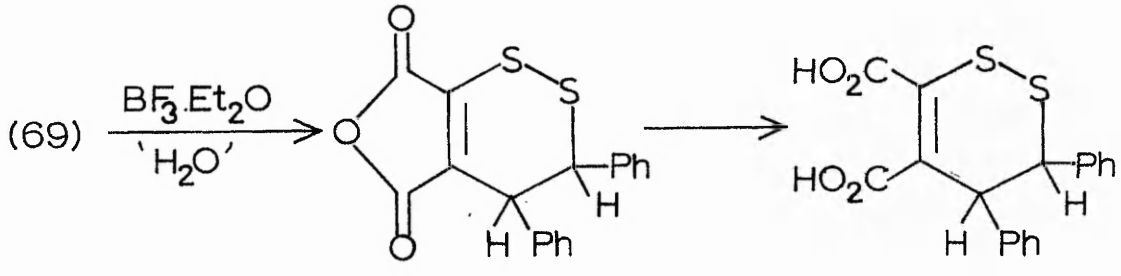


(69) (91)

Again, no evidence of diacid formation was found.

The o-dithiin diester, 69,was found to be remarkably resistant to hydrolysis by strong acids, as was the equivalent m-dithiin.

The required o-dithiin diacid, 178,was eventually prepared (as in the m-dithiin series) via the corresponding anhydride, 179. When treated with boron trifluoride etherate in moist refluxing toluene for 2 hours, the diester, 69,was almost completely converted into the anhydride, 179 (for mechanism see page 87), which in turn was converted quantitatively into 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylic acid (178).



(179) (178)

As would be expected, the diacid, 178, underwent dehydration to regenerate the anhydride extremely readily when warmed.

Final success in activating the functional groups at C-5 and C-6 in these compounds opens the way for the preparation of many more interesting and novel *o*-dithiins, and provides a route, *via* desulphurisation to many more hitherto inaccessible 2,3-dihydrothiophens.

EXPERIMENTAL

SECTION INDEX TO EXPERIMENTAL PROCEDURES

GENERAL

Infrared spectra, except where stated, were recorded with potassium bromide discs using a Perkin Elmer 137 spectrometer. Ultraviolet spectra were recorded in methanol on a Perkin Elmer SP800 spectrometer.

Proton magnetic resonance spectra were recorded on a JEOL JNM C-60 HL 60 MHz spectrophotometer using tetramethylsilane as the internal standard in the solvents indicated.

^{13}C Magnetic resonance studies, mass spectral determinations and microanalyses were carried out by the Physical Methods Section of Imperial Chemical Industries Limited, Alderley Edge, Macclesfield, and two X-ray determinations were undertaken at the Naval Research Laboratory, Washington, D.C.

Melting points were obtained using open capillary tubes in an electrically heated Gallenkamp melting point apparatus and are uncorrected.

Thin-layer chromatography was carried out using pre-spread plates (5 x 20 cm: Polygram SIL/GUV 254 from Camlab, Cambridge). Wet column chromatography was carried out using Fison silica gel MFC (80-200 mesh) and dry column chromatography was carried out using Merck silica gel (7734) deactivated with 10% water. Except where stated, chromatographic separations were obtained using dichloromethane as the solvent.

Prior to use, solvents were dried over 4 or 5 Å molecular sieves, and organic solutions were dried over magnesium sulphate.

1. General Methods for the Preparation of m-Dithiins

Procedure A

The acetylenic ester (2 eq) was treated with the aromatic aldehyde (1 eq) and boron trifluoride etherate (1 eq) in dry toluene. Hydrogen sulphide gas was passed into the solution for 5 minutes, during which time a white precipitate of 2,4,6-triaryl-1,3,5-trithiane appeared. The reaction mixture was stirred and heated at 85° until the solid had dissolved (about 30 minutes). The solution was then allowed to cool, was washed with water and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a brown oil which crystallised on treatment with methanol. The product was filtered and recrystallised from methanol. (This procedure was initially applied to the preparation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a), but was found to be less effective than the alternative procedure, B, given below.)

Procedure B

i. The aromatic aldehyde (1 eq) and boron trifluoride etherate (3 eq) in toluene were treated with hydrogen sulphide gas for 5 minutes. The resulting crystals of 2,4,6-triaryl-1,3,5-trithiane were removed by filtration and washed with toluene.

ii. The above trithiane (1 eq) in dry toluene was treated with boron trifluoride etherate (3 eq). The mixture was stirred and heated at 85° until the solid had dissolved (10 minutes) and dimethyl acetylenedicarboxylate (DMAD) or methyl propiolate

(3 eq) was added dropwise over a period of 15 minutes. The solution was heated for a further 10 minutes, cooled, washed with water and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow oil which was triturated with petroleum ether (bp.40-60°) to remove the excess of acetylenic ester. The residual oil crystallised readily on treatment with methanol.

The following trithianes were prepared according to procedure B.i.:

2,4,6-Triphenyl-1,3,5-trithiane (71)

Benzaldehyde (3.18g, 30mmol), when treated with hydrogen sulphide in toluene (20 ml) gave the trithiane, 71, as colourless needles (3.4g, 93%); mp.225-226° (lit.[192] 225°).

2,4,6-Tri-p-chlorophenyl-1,3,5-trithiane

p-Chlorobenzaldehyde (4.22g, 30mmol), in toluene (20 ml) gave the trithiane as colourless needles (4.0g, 85%); mp.189-191° (lit.[194] 189-190°).

2,4,6-Tri-p-tolyl-1,3,5-trithiane

p-Tolualdehyde (3.60g, 30mmol) in toluene (20 ml) gave the trithiane as colourless needles (3.3g, 81%); mp.179-181° (lit.[74] 180°).

2,4,6-Tri-p-anisyl-1,3,5-trithiane

p-Anisaldehyde (4.08g, 30mmol) in toluene (20 ml) gave the trithiane as colourless needles (3.6g, 79%); mp.182-184° (lit.[196] 180°).

The following m-dithiins were prepared according to procedure B.ii.:

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)

2,4,6-Triphenyl-1,3,5-trithiane (0.37g, 1.0mmol), dimethyl acetylenedicarboxylate (0.43g, 3.0mmol) and boron trifluoride etherate (1.0 ml) in toluene (15 ml) gave the dithiin, 70a, as colourless needles (0.29g, 74%); mp.157° (lit.[71] 157°), M/e 386.

(Table 1, page 47, contains a list of spectroscopic data for 70a; bond lengths and angles calculated during X-ray crystallographic analysis are given in Appendix A.)

Methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b)

Trithiane, 71 (0.37g, 1.0mmol), methyl propiolate (0.25g, 3.0mmol) and boron trifluoride etherate (1.0 ml) in toluene (15 ml) gave the dithiin, 70b, as colourless needles (0.2g, 62%); mp.130-132° (lit.[71] 133°), M/e 328.

Dimethyl 2,4-di-p-chlorophenyl-4H-m-dithiin-5,6-dicarboxylate (70c)

m-Dithiin, 70c (56%), crystallised as pale yellow cubes; mp.146-148°. (Found: C,52.4; H,3.5; S,14.4. $C_{20}H_{16}Cl_2O_4S_2$ requires C,52.7; H,3.5; S,14.1%), M/e 455.

δ,ppm($CDCl_3$): 7.60 (m, C_6H_4)
5.59 (s, H-2), 4.93 (s,H-4)
4.04, 3.83 (s,CO_2CH_3)

ν max, cm^{-1}: 1720 (CO_2Me)

(The yield of 70c was improved by only 8% when the product remaining in the mother liquor was isolated by dry column chromatography.)

Dimethyl 2,4-di-p-tolyl-4H-m-dithiin-5,6-dicarboxylate (70d)

m-Dithiin, 70d, crystallised as off-white hexagons (28%) and had mp.135-138°. (Found: C,63.2; H,5.3; S.15.4. $C_{22}H_{22}O_4S_2$ requires C,63.8; H,5.3; S,15.5%.)

^{1}Hnmr, δ ,ppm ($CDCl_3$): 7.11 (s,C_6H_4)
5.34 (s,H-2), 4.78(s,H-4)
3.84, 3.62 (s,CO_2CH_3)
2.29, 2.25 (s, $ArCH_3$)

ν max, cm^{-1}: 1730, 1714, (CO_2Me)

^{13}Cnmr, δ ,ppm ($CDCl_3$): 146.0(C-6),121.3(C-5),
45.7(C-4),45.1(C-2)

Dimethyl 2,4-di-p-anisyl-4H-m-dithiin-5,6-dicarboxylate (70e)

m-Dithiin, 70e, crystallised as off-white prisms (24%) and had mp.126-127°. (Found: C,59.5; H,5.1; S,14.2. $C_{22}H_{22}O_6S_2$ requires C,59.2; H,4.9; S,14.3%)

δ ,ppm ($CDCl_3$): 7.25 (m, C_6H_4)
5.53, (s,H-2), 4.94(s,H-4)
3.99, 3.77 (s,CO_2CH_3)
3.90, 3.89 (s,$ArOCH_3$)

ν max, cm^{-1}: 1728, 1701 (CO_2Me)

2. General Procedure for Metalation and Ring Substitution of m-Dithiins

The m-dithiin (1 eq) dissolved in dry tetrahydrofuran, was stirred magnetically at -50° under an atmosphere of dry nitrogen. A 1.6 molar hexane solution of n-butyllithium (1 eq) was added dropwise from a syringe over a period of 5 minutes, and the orange/red solution of lithiated m-dithiin was stirred at -50° for 1 hour. The electrophile (large excess) was then added (the addition generally resulted in a lightening in colour of the solution) and the solution was allowed to warm to room temperature and was stirred overnight. The THF was evaporated under reduced pressure and the residue was dissolved in dichloromethane, washed with dilute hydrochloric acid, water, and brine, then dried ($MgSO_4$). Removal of solvent in vacuo gave a yellow oil which crystallised on treatment with methanol. The product was filtered and recrystallised from methanol.

The following 6H-tautomeric m-dithiins were prepared using the above procedure:

Dimethyl 2,4-dipheny1-6H-m-dithiin-5,6-dicarboxylate (76a)

m-Dithiin, 70a (0.39g, 1.0mmol), was treated with n-butyllithium (1.0mmol). Dilute hydrochloric acid (20 ml) was added to the orange/red solution, whereupon, the colour changed instantly to yellow. The product, 76a (isolated as described above), crystallised from methanol as pale yellow prisms (0.33g, 85%) and had mp.101°. (Found: C,62.5; H,4.6; S,16.5. $C_{20}H_{18}O_4S_2$ requires C,62.2;

H,4.7; S,16.6%), $^{M}/e$ 386.

(Table 1, page 47, contains a list of spectroscopic data for 76a; bond angles and lengths determined by X-ray crystallographic analysis are given in Appendix A.)

Dimethyl 6-deutero-2,4-diphenyl-6H-m-dithiin,5,6-dicarboxylate (76b)

m-Dithiin, 70a (0.39g, 1.0mmol), after lithiation, was treated with deuterium oxide (2 ml). On stirring overnight, the solution had become pale yellow in colour, and (after the usual work-up procedure) the deuterated m-dithiin, 76b, crystallised as yellow prisms (0.34g, 87%); mp.109-111°, $^{M}/e$ 387.

^{1}Hnmr, δ, ppm($CDCl_3$): 7.30 (s, C_6H_5)
5.53 (s, H-2)
3.78, 3.38 (s, CO_2CH_3)

^{13}Cnmr, δ, ppm($CDCl_3$): 154.7(C-6), 115.6(C-5),
47.8(C-4), 45.1(C-2)

Dimethyl 6-methyl-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76c)

m-Dithiin, 70a (0.39g, 1.0mmol), was lithiated as previously described, then methyl iodide (2.8g, 20mmol) was added to the orange/red solution. The 6-methyl m-dithiin, 76c (0.34g, 85%), crystallised from methanol as pale yellow prisms and had mp.110°. (Found: C,62.9; H,5.1. $C_{21}H_{20}O_4S_2$ requires C,63.0; H,5.0%), $^{M}/e$ 400.

δ,ppm($CDCl_3$): 7.23 (s,C_6H_5)
5.69 (s, H-2)
3.84, 3.30 (s,CO_2CH_3)
1.71 (s,$-CH_3$)

νmax,cm^{-1}: 1730, 1711 (CO_2Me)

λmax, nm (methanol): 226(ε14800), 274(ε6400)

(Dimethyl sulphate was tried as an alternative methylating agent, but this provided no advantage over methyl iodide.)

Dimethyl 6-acetyl-2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76d)

m-Dithiin, 70a (0.39g, 1.0mmol), was lithiated in the usual manner, and acetic anhydride (0.5g, 5.0mmol; – distilled) was added to the dark solution. A yellow colour was apparent after several hours, and the product, 76d, was isolated after the work-up (which was supplemented by an extra aqueous and a bicarbonate wash) as colourless prisms (0.064g, 15%); mp.116-118°. (Found: C,62.6; H,4.4. $C_{22}H_{20}O_5S_2$ requires C,61.7; H,4.7%), M/e 428.

δ,ppm($CDCl_3$): 7.37 (s, C_6H_5)
5.35 (s, H-2)
3.87, 3.31 (s,CO_2CH_3)
2.56 (s,$COCH_3$)

νmax, cm^{-1}: 1748, 1710 (CO_2Me)
1725 (COMe)

(Redistilled acetyl chloride was used to acetylate the anion as an alternative to acetic anhydride, but the acid chloride contained enough hydrogen chloride on each occasion to yield the protonated product, 76a, in preference to the

6-acetyl m-dithiin, 76d.)

Attempted allylation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)

The lithio-derivative of m-dithiin 70a (0.39g, 1.0mmol) was treated with freshly distilled allyl bromide (0.6g, 5.0mmol). No lightening of colour occurred, and work-up as before resulted in a brown oil which could not be crystallised. Although the reaction mixture was complex, preparative scale thin-layer chromatography permitted separation of a major component which was shown (nmr) to consist of both allylated and protonated material.

Attempted benzylation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)

m-Dithiin, 70a (0.39g, 1.0mmol), was lithiated in the normal way and benzyl bromide (0.26g, 1.5mmol) was added to the orange/red solution. A brown oil was produced after the usual work-up and ^{1}Hnmr spectroscopic analysis indicated that no benzylation had occurred.

Attempted acylation of the lithio-m-dithiin with propionyl chloride

A solution of lithiated m-dithiin, 70a (0.39g, 1.0mmol), was treated with propionyl chloride (0.46g, 5.0mmol). A yellow oil resulted, which could not be crystallised, and was shown (nmr) to consist mainly of 6H-m-dithiin, 76a.

Attempted carboxylation of the lithio-m-dithiin

i. Solid carbon dioxide was used to quench the anion produced by the lithiation of m-dithiin

70a. Isolation of the product in the usual fashion gave a yellow oil, which was found to contain none of the required m-dithiin carboxylic acid on bicarbonate extraction.

ii. A stream of dry carbon dioxide gas was bubbled through a solution of lithiated m-dithiin for several hours at room temperature, but as before, no acidic material was produced. Thin-layer chromatography indicated that a multicomponent mixture was present.

Reaction of the lithio-m-dithiin with 2-chloroethyldimethylamine

m-Dithiin, 70a (0.39g, 1.0mmol), lithiated as described earlier (page 158) was treated with a solution of 2-chloroethyldimethylamine (0.16g. 1.5mmol) in tetrahydrofuran (5 ml). No change of colour was observed in the solution, and after standing at room temperature for 20 hours, the solvent was removed in vacuo and the residue dissolved in dichloromethane. The solution was washed with dilute hydrochloric acid, sodium bicarbonate, water, and finally dried ($MgSO_4$). (The acidic washings were made basic, extracted with dichloromethane and shown (nmr) to contain no substituted m-dithiin.) The dark residue obtained above (0.28g) could not be crystallised, and was shown by thin-layer chromatography to consist of several components.

Treatment of *m*-dithiin, 70a, with 2 equivalents of *n*-butyllithium

A solution of dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry THF (100 ml) was treated (under normal lithiation conditions) with 2 molar equivalents of *n*-butyllithium, then deuterium oxide (2 ml). Thin-layer chromatography indicated that the resulting mixture contained many components, and no crystalline product could be isolated.

3. Proof of Position of Lithiation in m-Dithiins

Ozonolysis of dimethyl 6-deutero-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76b)

Monodeuterto m-dithiin, 76b (0.39g, 1.0mmol), was dissolved in dichloromethane (40 ml). The solution was stirred and cooled to -78° and ozone was bubbled through for 20 minutes after which time a blue colour had developed. The solution was allowed to warm to room temperature and thin-layer chromatography indicated that a complex mixture was present which did not appear to contain any unchanged starting material. Evaporation of the solvent under reduced pressure gave an orange residue which smelled strongly of benzaldehyde; steam distillation of the residue followed, and the distillate was warmed briefly with an acidic solution of 2,4-dinitrophenylhydrazine in methanol. Orange crystals of benzaldehyde-2,4-dinitrophenylhydrazone appeared on cooling and were removed by filtration (0.13g, 45%); mp.235° (lit.[197] 237°). The product was shown to be identical with an authentic sample (mixed melting point). The mass spectrum from the product indicated that greater than 90% of the benzaldehyde-2,4-dinitrophenylhydrazone was undeuterated.

Dethioacetalisation of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) with mercuric oxide-mercuric chloride[25]

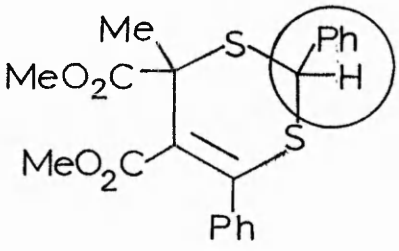
m-Dithiin, 70a (0.39g, 1.0mmol), was dissolved with warming in methanol:water/9:1 (40 ml). A suspension of yellow mercury (II) oxide (0.20g, 0.45mmol) and mercury (II) chloride (0.55g, 2.0mmol) in the same solvent (10 ml) was

added to the stirred solution. A white precipitate was produced and the mixture was heated under reflux for four and a half hours, during which time the yellow colour of the mercury (II) oxide disappeared. The suspension was then allowed to cool, and the white precipitate was removed by filtration and discarded. Methanol (30 ml) was distilled from the filtrate through a Vigreux column and the residue was added to dichloromethane:pentane/1:1 (20 ml). The solution was then washed with aqueous ammonium acetate (50 ml), brine (50 ml), and dried. The solvent was evaporated under reduced pressure to give an oily solid (0.2g). The solid fraction was shown to be unchanged starting material (nmr) and the residual oil was dissolved in methanol (2 ml) and added to an acidic solution of 2,4-dinitrophenylhydrazine in methanol which was warmed briefly then allowed to cool. Orange crystals of benzaldehyde-2,4-dinitrophenylhydrazone were obtained (0.07g, 26%) which were identified by mixed melting point and mass spectroscopy; $^{M}/e$ 286.

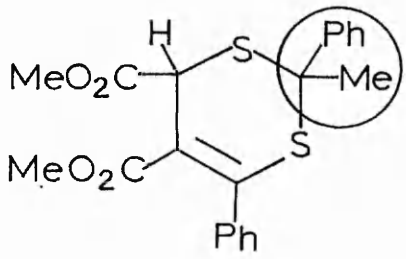
Dethioacetalisation of dimethyl 6-methyl-2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76c)

The 6-methyl *m*-dithiin, 76c (0.40g,1.0mmol), was treated as described in the preceding experiment for *m*-dithiin, 70a, except that the reaction was monitored for disappearance of starting material by thin-layer chromatography. It was found that heating for 12 hours under reflux was required before the starting material was consumed (and a significant amount of the product aldehyde had formed). The presence of an aldehyde was

confirmed by spraying the thin-layer chromatogram with an acidic solution of 2,4-dinitrophenylhydrazine in methanol. Work-up as before gave orange crystals of benzaldehyde-2,4-dinitrophenylhydrazone (0.1g, 37%) (which was again identified by mixed melting point and mass spectroscopy; $^{M}/_{e}$ 286). No acetophenone-2,4-dinitrophenylhydrazone was observed (as would have been expected, had the starting material been the C-2 methyl m-dithiin, 76c').



(76c)

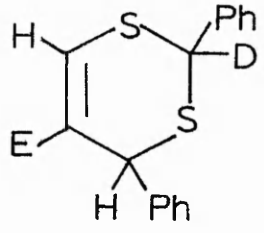


(76c')

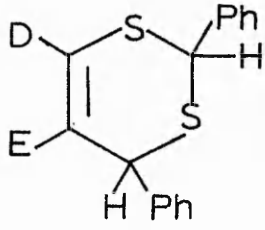
4. Reactions of Other m-Dithiins with n-Butyllithium

Lithiation and subsequent alkylation of m-dithiin monoester, 70b

Methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b; 0.33g, 1.0mmol) was treated with a 1.6 molar hexane solution of n-butyllithium (0.63 ml, 1.0mmol) using the same conditions as those used to deprotonate m-dithiin 70a. Treatment of the lithio-m-dithiin with deuterium oxide (2 ml) yielded, after the normal isolation procedure, a brown oil which could not be crystallised. This was shown (nmr) to be a mixture of material which had been deuterated at C-2 (78b) (one of the benzylic positions) and at C-6 (78a) (the vinylic position), the latter being the major product.



(78b) 2 : 3



(78a)

E = CO_2Me

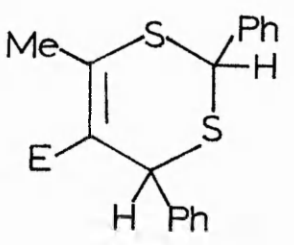
When the experiment was repeated using methyl iodide in place of deuterium oxide, methyl 6-methyl-2,4 diphenyl-4H-m-dithiin-5-carboxylate (78) was isolated as colourless prisms (0.04g, 12%) and had mp. 151-154°, M/e 342. (No material methylated at C-2 was obtained.)

δ, ppm($CDCl_3$): 7.31 (s, C_6H_5)

5.53 (s, H-2), 4.72 (s, H-4)

3.66 (s, CO_2CH_3)

2.50 (s, $-CH_3$)



(78)

νmax, cm^{-1}: 1708 (CO_2Me)

Attempted lithiation of 6-methyl *m*-dithiin, 76c

A solution of dimethyl 6-methyl-2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76c; 0.40g, 1.0mmol) in dry tetrahydrofuran (100 ml) was treated with 1 equivalent of *n*-butyllithium at -60° in the usual way. Deuterium oxide (2 ml) was added, and after work-up, a brown oil (0.35g) was obtained which was shown (nmr) to be a mixture containing unreacted starting material; no deuterated *m*-dithiin was observed.

The experiment was repeated at temperatures of -40° and -78°; the former gave a multicomponent mixture containing no starting material, and the latter gave only unchanged 76c.

Lithiation and deuteration of *m*-dithiin, 76a

Dimethyl 2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76a; 0.39g, 1.0mmol) was treated with 1 equivalent of *n*-butyllithium in the way described for previous *m*-dithiins (page 158). Half of the resulting dark solution was withdrawn after 1 hour and treated with excess deuterium oxide (1 ml). Dilute hydrochloric acid was added to the remainder, and after processing in the usual way, both samples were examined by ^{1}Hnmr spectroscopy. This clearly showed in the first sample that monodeuteration had occurred, and in the second, that unchanged starting material had been regenerated. Crystalline samples of monodeuterated *m*-dithiin, 76b, and 76a, were obtained in 76 and 89% yields respectively.

5. Lithiation of m-Dithiin, 70a, Using the Conditions of Biellmann et al[96]

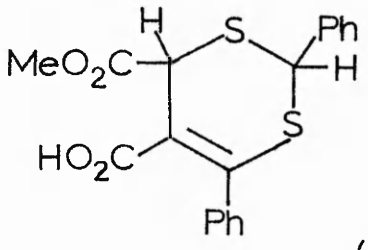
A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry tetrahydrofuran (40 ml) was stirred at -20° under an atmosphere of dry nitrogen. TMEDA (0.12g, 1.0mmol) was added, followed by a 1.6 molar hexane solution of n-butyllithium (0.63 ml, 1.0mmol), and stirring was continued at -20° for 1 hour. The reaction was then quenched with methyl iodide (0.5 ml, 3mmol) followed by an excess of water (20 ml). The mixture was partitioned between ether and water, and the organic layer was washed repeatedly with water and dried ($MgSO_4$). Evaporation of the solvent in vacuo, followed by treatment with ether (2 ml) afforded 6-methoxycarbonyl-2,4-diphenyl-6H-m-dithiin-5-carboxylic acid (84) as colourless needles (0.15g, 32%); mp.184-187° (gas evolved on melting). (Found: C,61.0; H,4.3. $C_{19}H_{16}O_4S_2$ requires C,61.3; H,4.3%), $^M/_e$ 372.

^{1}Hnmr, δ, ppm($CDCl_3$): 8.80 (s,CO_2H)
7.29 (s,C_6H_5)
5.56 (s,H-2), 5.01(s,H-6)
3.42 (s,CO_2CH_3)

ν max, cm^{-1}, (KBr): 1694 (CO_2Me), 1683(CO_2H)
(nujol): 1698 ("), 1684(")

^{13}Cnmr, δ, ppm:

DMSO	DMSO/Et_3N	Assignment
171.2	171.7	$\underline{CO_2}$Me at C-6
165.8	167.4	CO_2H
151.7	145.3$^{\not}$	C-4
117.2	121.9*	C-5



(84)

Dimethyl 2,4 diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a) was isolated as a second product from the mother liquor (0.26g, 46%), but when the experiment was repeated with the exclusion of methyl iodide, the acid, 84, was obtained in 62% yield, and no 76a was isolated. When the reaction was quenched with acid instead of water, 76a was the sole product (81%).

(It was found in this reaction, that TMEDA can be replaced with DABCO without adverse effect.)

Esterification of m-dithiin monoacid, 84, with diazomethane

6-Methoxycarbonyl-2,4-diphenyl-6H-m-dithiin-5-carboxylic acid (84; 0.37g, 1.0mmol) in dry ether (30 ml) was treated with an excess of ethereal diazomethane at 0°.

$^{\not}$ shift upfield

* shift downfield

The reaction was shown by thin-layer chromatography to be complete after 10 minutes, and the excess diazomethane was removed by warming the solution on a water bath. Removal of solvent *in vacuo*, followed by ^{1}Hnmr spectroscopic analysis indicated the presence of dimethyl 2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76a); this crystallised as yellow prisms on treatment with methanol (0.36g, 93%) and had mp.102°.

Attempted decarboxylation of *m*-dithiin monoacid, 84

i. 6-Methoxycarbonyl-2,4-diphenyl-6H-*m*-dithiin-5-carboxylic acid (84) was mixed intimately with ground glass. Heating of the mixture at 185° was followed almost immediately by the evolution of gas. This ceased after 10 minutes and the dark residue was dissolved in methanol. No crystalline product was produced and thin-layer chromatography indicated that the methanolic solution contained at least 7 components; this experiment was therefore abandoned.

ii. 6-Methoxycarbonyl-2,4-diphenyl-6H-*m*-dithiin-5-carboxylic acid (84; 0.37g, 1.0mmol) was heated under reflux in pyridine (15 ml) with copper (I) oxide (0.30g, 2.1mmol). Thin-layer chromatography showed after 1 hour that a multicomponent mixture was present, which still appeared to contain some starting material. The reaction afforded a dark oil which could not be crystallised.

6. Alternative Attempts at m-Dithiin Ring Proton Abstraction

Treatment of m-dithiin, 70a, with sodium hydride

A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry tetrahydrofuran (40 ml) was stirred at 0^{o} under a nitrogen atmosphere. An 80% dispersion of sodium hydride in paraffin wax (0.06g, 2.0mmol) was added and stirring was continued for 3 hours, during which time the characteristic orange/red colour had developed. Dilute hydrochloric acid (20 ml) was then added and the solution changed colour to pale yellow. Removal of solvent *in vacuo* gave an oil which was dissolved in dichloromethane and washed several times with water. The crude residue was shown (thin-layer chromatography; nmr) to contain at least 4 components including the tautomer, dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a). The main product was unchanged starting material, which crystallised (0.2g) on treatment with methanol.

N,N-Dimethylformamide (DMF) and toluene were also used as solvents for this reaction, with equally poor results.

Phase-transfer deprotonation of m-dithiin, 70a

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was dissolved, with warming, in dry benzene (30 ml); anhydrous potassium carbonate (1.38g, 10mmol) was then added, followed by benzyl tri-n-butylammonium bromide (BTBAB; 0.36g, 1.0mmol). The suspension (now yellow in colour) was stirred vigorously

and heated under reflux for 3 hours, after which time the potassium carbonate was filtered. The cooled solution was washed with dilute hydrochloric acid, water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resultant oil was shown (nmr) to be the tautomer, dimethyl 2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76a) which crystallised as yellow prisms when treated with methanol (0.32g, 83%) and had mp. 101°.

It was found that when less than a full equivalent of phase-transfer catalyst was used, the reaction time increased dramatically; e.g. 24 hours using 0.1mmol of catalyst.

Attempted phase-transfer ethylation of *m*-dithiin, 70a

A solution of dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry benzene (30 ml) was heated under reflux with freshly distilled ethyl iodide (0.72g, 5mmol), anhydrous potassium carbonate (1.38g, 10mmol) and BTBAB (0.36g, 1.0mmol). Samples were withdrawn at various intervals for analysis by thin-layer chromatography, and it was shown (nmr) that after 12 hours heating, all the starting material had tautomerised to 76a, but none had been ethylated. A 77% yield of the 6H-tautomer, 76a, was obtained; mp.101°.

Attempted phase-transfer deuteration of *m*-dithiin, 70a

Dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was treated with anhydrous potassium carbonate and BTBAB as described above. Reprotonation of a sample of the mixture, followed by nmr

spectroscopic analysis revealed that the 6H-tautomer, 76a, had formed. The remainder of the mixture was filtered and shaken with an excess of deuterochloric acid (5mmol). The residue obtained after the usual work-up procedure was shown (nmr) to contain no deuterated m-dithiin.

Attempted phase-transfer methylation of m-dithiin, 70a

A mixture of m-dithiin, 70a (0.39g, 1.0mmol), BTBAB (0.36g, 1.0mmol), anhydrous potassium carbonate (1.38g, 10mmol) and freshly distilled dimethyl sulphate (0.63g, 5mmol) were heated under reflux for 6 hours in dry benzene (30 ml). The reaction mixture was processed as before, and nmr spectroscopy indicated, somewhat surprisingly, that the starting material had neither tautomerised nor suffered methylation.

7. Oxidation of m-Dithiins

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was treated with the following oxidising agents:

a. m-Chloroperbenzoic acid (MCPBA)

Many variations in reaction conditions were made using MCPBA in order to achieve a clean, complete reaction. These included changing the quantity of MCPBA used, reaction time, reaction temperature, solvent, and pH. Details of these will not be described, but the following procedure was judged to be the most efficient:-

m-Dithiin, 70a (0.39g, 1.0mmol), was dissolved in dichloromethane (15 ml) at 0^{o} and 85% MCPBA (0.24g, 1.2mmol) was added. Analysis by thin-layer chromatography after 5 minutes showed that a 3 component mixture had formed, but that all starting material had disappeared. The pale yellow solution was washed with saturated $NaHCO_3$ (3 times) with brine, then dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave a yellow oil which crystallised as colourless prisms (mp.143-144^{o}) on treatment with methanol. The product, 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b) was purified by recrystallisation from methanol (0.23g, 58%). (Found: C.59.5; H,4.5. $C_{20}H_{18}O_5S_2$ requires C,59.7; H,4.5%), M/e 402.

^{1}Hnmr, δ, ppm:

	$CDCl_3$	C_6D_6
7.21	(s,C_6H_5)	7.02
5.70,4.48	(s,H-2,H-4)	5.70,4.45
3.98,3.75	(s,CO_2Me)	3.66,3.20

ν max, cm^{-1}:	1744, 1712 (CO_2Me)
λ max, nm (MeOH):	219 (ε 14300), 286 (ε 6200)
^{13}Cnmr, δ, ppm ($CDCl_3$):	144.7 (C-6), 117.0 (C-5), 63.8 (C-4), 55.6 (C-2)

^{1}Hnmr analysis of the product before recrystallisation showed two extra CHPh singlet absorptions at δ 5.53 and 4.67ppm respectively; this is indicative of the presence of a mixture of sulphoxide isomers. An attempt was made to separate this mixture (ratio 3:1) by dry column chromatography and thus isolate the minor component.

In this way, the minor sulphoxide isomer, 87a, (see page 61) was isolated in 6% overall yield from m-dithiin 70a; mp.144°. (Found: C,59.9; H,4.5; S,16.0. $C_{20}H_{18}O_5S_2$ requires C,59.7; H,4.5; S,15.9%.)

^{1}Hnmr, δ, ppm:	$CDCl_3$	C_6D_6
	7.21 (s, C_6H_5)	7.02
	5.53, 4.67 (s, H-2, H-4)	5.37, 4.70
	3.98, 3.75 (s, CO_2Me)	3.66, 3.20

ν max, cm^{-1}:	1731, 1710 (CO_2Me)
λ max, nm (MeOH):	224 (ε 14500), 283 (ε 6350)
^{13}Cnmr, δ ppm ($CDCl_3$):	142.8 (C-6), 112.3 (C-5), 60.0 (C-4), 57.5 (C-2)

b. MCPBA-sodium hydrogen phosphate

A solution of dichloromethane (15 ml) containing dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was stirred at room temperature with sodium hydrogen phosphate (0.14g, 1.0mmol) and MCPBA (0.24g,

1.2mmol). It was shown by thin-layer chromatography that the reaction was over after about five minutes; the sodium hydrogen phosphate was filtered, and the solution was washed twice with a solution of sodium bicarbonate. Removal of solvent *in vacuo* gave a yellow oil which yielded 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-*m*-dithiin-3-oxide(*87b*) as colourless prisms(0.14g, 35%); mp.143°. None of the minor isomer, *87a*, was isolated, and it would appear that the inclusion of sodium hydrogen phosphate has little effect on the reaction (except to reduce the yield slightly).

c. *Sodium metaperiodate*

Solvents used for this reaction in conjunction with water included methanol, acetone, tetrahydrofuran, acetonitrile and glacial acetic acid. It most cases, no detectable reaction took place (thin-layer chromatography) even when extended reaction times were used. Partial sulphoxide formation was observed however, when the reactants were heated in glacial acetic acid for 3 hours at 50° as outlined below.

Dimethyl 2,4-diphenyl-4H-*m*-dithiin 5,6-dicarboxylate (*70a*; 0.39g, 1.0mmol) was dissolved with warming in glacial acetic acid (25 ml). The solution was stirred at room temperature, and sodium metaperiodate (0.86g, 4.0mmol) in water (2 ml) was added. Analysis by thin-layer chromatography after 1 hour showed that no reaction had occurred. The solution was heated at 50° for 3 hours, after which time a mixture had formed. The

solution, after cooling, was diluted with water (100 ml) and extracted with dichloromethane. The combined extracts were washed twice with sodium bicarbonate, with brine, then dried. Evaporation of the solvent under reduced pressure gave a yellow oil which crystallised as colourless prisms on treatment with methanol. The product, 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-*m*-dithiin-3-oxide (87b; 0.12g, 29%) had mp.144°, and was shown to be identical to previous samples (nmr; mixed melting point).

d. Periodic acid

Dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was heated under reflux in acetonitrile (30 ml) with a solution of periodic acid (0.29g, 1.5mmol) in water (2 ml) for 3 hours. No change in the starting material was detected after this period.

The experiment was repeated with ether (50 ml) as solvent and again no reaction could be detected, this time after refluxing for 6 hours.

e. Phase-transferred periodate ion

(Potassium periodate/benzyl triethylammonium chloride; BTEAC)

A solution of *m*-dithiin, 70a (0.39g, 1.0mmol), in dichloromethane (15 ml) was stirred vigorously with a saturated solution of potassium periodate (20 ml). BTEAC (0.19g, 1.0mmol) was added, and stirring was continued for 2 days after which time most of the starting material remained unchanged.

f. Tetrabutylammonium periodate

Periodic acid (1.92g, 10mmol) was dissolved in water (25 ml) and added to a stirred solution of tetrabutylammonium hydroxide (2.59g, 10mmol) in water (25 ml). Tetrabutylammonium periodate precipitated as a dense white solid; this was removed by filtration, recrystallised (dichloromethane:ether/2:3) and dried (1.4g, 44%); mp.182-183°.

A solution of dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) and tetrabutylammonium periodate (0.64g, 2.0mmol) in dichloromethane (25 ml) was stirred at room temperature for 48 hours. None of the *m*-dithiin had reacted after this period of time.

g. Hydrogen peroxide

(Ethyl acetate was found to be a better solvent for this reaction than acetone, methanol or acetonitrile.)

m-Dithiin, 70a (0.39g, 1.0mmol), was dissolved in ethyl acetate (30 ml). A 50% solution of hydrogen peroxide (0.27g, 4.0mmol) was added, and the reaction was found (thin-layer chromatography) to be complete after 4 days at room temperature. The solution was washed with aqueous ferrous sulphate (until a negative starch-iodide test was obtained) then dried; the solvent was evaporated under reduced pressure to give a yellow oil which crystallised on treatment with methanol. The colourless prisms, as before, were shown (nmr) to be a mixture of sulphoxide isomers (3:1). The major isomer, 87b, was

purified by repeated crystallisation from methanol (0.2g, 51%) mp.143°; the minor monosulphoxide isomer could not be isolated from the mixture in a pure state.

h. Hydrogen peroxide-ammonium molybdate[119]

m-Dithiin, 70a (0.39g, 1.0mmol), was dissolved with slight warming in methanol:dichloromethane/3:1 (40 ml) and a 50% solution of hydrogen peroxide (0.27g, 4.0mmol) was added dropwise. A trace of ammonium molybdate was added, and the solution was heated under reflux for 5 hours during which time all of the starting material was consumed. The solution was diluted with water (100 ml) and extracted with dichloromethane. The combined extracts were then washed with aqueous ferrous sulphate (until a negative starch-iodide test was observed) with water, then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave a yellow oil which crystallised on treatment with methanol. The product, 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b) was purified by a single recrystallisation from methanol, and shown to be identical (mixed melting point) with previous samples (0.26g, 62%), mp.144°.

i. Potassium permanganate

A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in acetone (30 ml) was stirred at 0°. Powdered potassium permanganate (0.47g, 3.0mmol) was added, and stirring was continued for 10 days, after which time none of the starting material had reacted. The mixture was heated under reflux for 5 hours, but no

reaction took place.

j. Phase-transferred permanganate ion

(18-crown-6 catalyst)

m-Dithiin 70a (0.39g, 1.0mmol) was dissolved in dichloromethane (20 ml) and powdered potassium permanganate (0.31g, 2.0mmol) was added, followed by 1 drop of water. The mixture was stirred vigorously with 18-crown-6 (0.01g, 0.04mmol) for 48 hours, but no change in the starting material was observed.

k. Sodium chlorite-pyridine-hydrochloric acid (trace)

A solution of m-dithiin 70a (0.39g, 1.0mmol) dissolved in pyridine:water:conc.HCl/100:20:0.5 (40 ml), was stirred at 25°. A solution of 80% sodium chlorite (0.09g, 1.0mmol) in water (2 ml) was added dropwise, while keeping the temperature below 50°. The reaction mixture was then heated at 80° for 1½ hours during which time a mixture containing several components had formed, but all the starting material had not been consumed (thin-layer chromatography).

The reaction was repeated at room temperature, and a similar mixture was formed after 6 hours.

l. Chromium trioxide-pyridine complex

Pyridine (1.0 ml, 12mmol) and dichloromethane (5 ml) were stirred together and cooled to 5°; chromium (VI) oxide (0.60g, 6mmol) was added and a yellow precipitate appeared. The solution was stirred at 5° for 5 minutes then allowed to warm to room temperature over 30 minutes. The red colour of the chromium trioxide-pyridine complex appeared during this period of time.

m-Dithiin, 70a (0.39g, 1.0mmol), in dichloromethane (6 ml) was stirred at room temperature for 20 minutes with the above chromium trioxide-pyridine complex. A black solid formed during this period of time and a portion of the mixture was removed, washed with water, and analysed by thin-layer chromatography. Some of the starting material had reacted to give a more polar component, but further analysis after 2 and 4 hours' stirring indicated that no further reaction had taken place. (This may have been due to the coating of the oxidant by the black solid which had been formed during the reaction.) An attempt was made to separate the mixture by column chromatography but the quantity of the new, more polar component obtained was insufficient for a positive identification to be made.

m. Iodosobenzene

Phenyl iodosodiacetate (3.22g, 10mmol) was added slowly to a vigorously stirred solution of 2 normal sodium hydroxide (22.5 ml, 45mmol). A pale green solid was formed; this was crushed thoroughly and the reaction mixture was left standing in the aqueous solution for 50 minutes. Water (10 ml) was added, and the solid iodosobenzene was removed by filtration, washed with cold water and dried in a vacuum desiccator (0.9g, 41%); mp.217° (lit.[117] 210°).

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) and iodosobenzene (0.22g, 1.0mmol) were heated at 100° in toluene (25 ml).

The reaction was monitored by thin-layer chromatography, and it was found that no reaction had occurred after heating for 6 hours. A further equivalent of iodosobenzene was added, and the solution was heated under reflux for 6 hours; again it was found that none of the starting material had reacted.

The following 6H-tautomeric m-dithiin monosulphoxides were prepared using method 'a', page 175:-

5,6-Dimethoxycarbonyl-2,4-diphenyl-6H-m-dithiin-1-oxide (90a)

Dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a; 0.39g, 1.0mmol) was reacted with MCPBA (0.24g, 1.2mmol). The product, 90a, crystallised from methanol as colourless prisms (0.21g, 51%) and had mp.155-156°. (Found: C,59.6; H.4.5. $C_{20}H_{18}O_5S_2$ requires C,59.7; H,4.5%), $^M/_e$ 402.

δ,ppm($CDCl_3$): 7.31 (s,C_6H_5)
5.37, 4.97 (s,H-2,H-4)
3.78, 3.37 (s, CO_2Me)

6-Deutero-5,6-dimethoxycarbonyl-2,4-diphenyl-6H-m-dithiin-1-oxide (90b)

Dimethyl 6-deutero-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76b; 0.39g, 1.0mmol) was reacted with MCPBA (0.24g, 1.2mmol). The product, 90b, crystallised from methanol as colourless prisms (0.09g, 23%) and had mp. 152°, $^M/_e$ 403.

δ,ppm($CDCl_3$): 7.28 (s, C_6H_5)
5.35 (s, H-2)
3.74, 3.32 (s, CO_2Me)

8. Reduction of m-Dithiins

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a) was treated with the following reducing agents:

a. Borane-tetrahydrofuran complex

m-Dithiin, 70a (0.39g, 1.0mmol), was dissolved in dry tetrahydrofuran (30 ml) and molar borane-THF complex (1.5 ml, 1.5mmol) was added. The solution was stirred overnight at room temperature, then heated under reflux for 3 hours; no reaction had taken place after this period of time and all of the starting material was recovered.

b. Borane-dimethyl sulphide complex (BMS)

A solution of m-dithiin, 70a (0.39g, 1.0mmol), in dry tetrhydrofuran (30 ml) was treated with 10 molar BMS (0.5 ml, 5.0mmol). Again, no reaction had taken place after several hours heating under reflux, and the starting material was quantitatively recovered.

c. Lithium borohydride

Lithium borohydride (0.05g, 2.0mmol) was added to a stirred solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry THF (30 ml). The reaction mixture was heated under reflux for 1 hour after which time all the starting material had been consumed (thin-layer chromatography). Water (20 ml) was added to the solution, and the THF was evaporated in vacuo. The aqueous fraction was then extracted with dichloromethane, washed with dilute hydrochloric acid, with water, and

dried ($MgSO_4$). The resultant brown oil was shown by thin-layer chromatography to be a mixture of 2 or 3 extremely polar components; ir and nmr spectroscopic analysis of the crude mixture indicated the absence of any carbonyl absorption and the presence of a strong hydroxyl absorption (3320 cm^{-1}). Attempts were made to purify the mixture by column and preparative thin-layer chromatography, but these were unsuccessful.

d. Lithium aluminium hydride

(Moisture was rigorously excluded from all apparatus.)

A solution of lithium aluminium hydride (0.08g, 2.0mmol) in dry THF (10 ml) was cooled below 0^o and stirred mechanically. m-Dithiin, 70a (0.39g, 1.0mmol), dissolved in the same solvent (30 ml) at 0^o was added dropwise over a period of 25 minutes. The starting material was shown (thin-layer chromatography) to have been consumed after 30 minutes at 0^o and a mixture of several components had formed. Excess lithium aluminium hydride was destroyed by the careful addition (with vigorous stirring) of cold water (10 ml) followed by dilute hydrochloric acid (10 ml). The reaction mixture was then processed as outlined in the preceeding experiment, affording a yellow oil (0.31g). Purification by column chromatography led to the isolation and characterisation of the main component as 2,4-diphenyl-6-methyl-4H-m-dithiin-5-carboxaldehyde (95; 0.09g, 22%), which crystallised from ether as colourless needles and had mp.151-152^o. (Found: C,68.8; H,5.2; S,21.0. $C_{18}H_{16}OS_2$ requires C,69.2; H,5.1; S,20.5%), ^{M}/e 312.

δ ,ppm($CDCl_3$):	10.14 (s,CHO)
	7.24 (s,C_6H_5)
	4.77 (s,H-2),4.63(s,H-4)
	2.36 (s,-CH_3)
ν max, cm^{-1}:	1657 (HC=O)

9. General Methods for the Preparation of o-Dithiins

Procedure A

The m-dithiin diester was heated under an atmosphere of dry nitrogen at 190°. The reaction was shown to be complete after 25 minutes by nmr spectroscopic analysis and the product o-dithiin crystallised when the cooled residue was treated with methanol.

Procedure B

The m-dithiin diester was dissolved in the minimum quantity of o-dichlorobenzene and heated under reflux for approximately 30 minutes. It was shown (nmr) that the reaction was complete after this period and most of the solvent was removed in vacuo. The residue was absorbed on to a silica gel column (Brockmann Grade I) and traces of o-dichlorobenzene were removed by elution (under suction) with petroleum ether (bp.40-60°). The product was obtained by eluting the column with methanol, and subsequently evaporating the eluate under reduced pressure; the o-dithiin (trans isomer only) crystallised during the latter operation.
(An alternative method of work-up involves diluting the reaction mixture with a large volume of petroleum ether (bp.40-60°); frequently, the product crystallises on standing.)

Procedure C

The m-dithiin diester was heated under reflux in xylene for 4 hours after which time the reaction was shown (nmr) to be complete. Removal of solvent in vacuo

afforded a brown oil which crystallised on treatment with methanol. The product o-dithiin was obtained as the trans isomer only.

The following o-dithiins were prepared according to the method specified in each case:

Dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69)

(Procedure A)

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was heated at 190° for 25 minutes. The product (trans isomer, 69) crystallised as pale yellow cubes on treatment with methanol (0.32g, 84%) and had mp. 109-111° (lit.[71] mp.113°).

Colourless needles of the cis o-dithiin isomer, 69a, crystallised from the methanolic mother liquors (0.02g, 3%); these were purified by fractional crystallisation from acetone, and had mp.91-92°. (Found: C,61.9; H,4.7. $C_{20}H_{18}O_4S_2$ requires C,62.2; H,4.7%), $^M/e$ 386. (A full comparison of the spectroscopic data for the cis and trans o-dithiins 69a and 69 is given in Table 5, page 116.)

Dimethyl 3,4-di-p-chlorophenyl-3,4-dihydro-o-dithiin-5,6-dicarboxylate (69c)

(Procedure B)

Dimethyl 2,4-di-p-chlorophenyl-4H-m-dithiin-5,6-dicarboxylate (70c; 0.46g, 1.0mmol) was heated under reflux in o-dichlorobenzene (5.0 ml) for 1 hour. The solvent was removed under reduced pressure and the product crystallised as pale yellow cubes (mp.106-107°) on

treatment with methanol (0.29g, 63%). (Found: C,52.5; H,3.4. $C_{20}H_{16}Cl_2O_4S_2$ requires C,52.7; H,3.5%.)

δ ,ppm($CDCl_3$):	7.14 (m,C_6H_4)
	4.39,4.21(d,H-3,H-4,J=6.5Hz)
	3.82,3.51 (s,CO_2CH_3)
ν max,cm^{-1}:	1730, 1722 (CO_2Me)

Dimethyl 3,4-dihydro-3,4-di-p-tolyl-o-dithiin-5,6-dicarboxylate (69d)

(Procedure C)

Dimethyl 2,4-di-p-tolyl-4H-m-dithiin-5,6-dicarboxylate (70d; 0.41g, 1.0mmol) was heated under reflux in xylene (5.0 ml) for 5 hours. The solvent was removed under reduced pressure, and the product crystallised as colourless needles on treatment with methanol (0.15g, 36%); mp.123-125°. (Found: C,63.5; H,5.5; S,15.6. $C_{22}H_{22}O_4S_2$ requires C,63.8; H,5.3; S,15.5%.)

δ ,ppm($CDCl_3$):	7.05 (m,C_6H_4)
	4.43,4.28(d,H-3,H-4,J=6.0Hz)
	3.83,3.49(s,CO_2CH_3)
ν max,cm^{-1}:	1725, 1720 (CO_2Me)

Methyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5-carboxylate (69b)

(Procedure A)

Methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b; 0.33g, 1.0mmol) was heated at 190° for 2 hours. o-Dithiin, 69b, crystallised as colourless cubes from methanol (0.18g, 56%) and had mp.128-129°. (Found: C,65.7; H,4.8; $C_{18}H_{16}O_2S_2$ requires C,65.8; H,4.9%),

M/e 328.

δ ,ppm($CDCl_3$):	8.01 (s,H-6)
	7.14 (m, C_6H_5)
	4.45, 4.20 (d,H-3,H-4,J=4.5Hz)
	3.56 (s, CO_2CH_3)
νmax, cm^{-1}:	1700 (CO_2Me)

Attempted preparation of dimethyl 3,4-di-p-anisyl-3,4-dihydro-o-dithiin-5,6-dicarboxylate (69e)

(Procedure B)

Dimethyl 2,4-di-p-anisyl-4H-m-dithiin-5,6-dicarboxylate (70e; 0.45g, 1.0mmol) was heated under reflux in o-dichlorobenzene (5.0 ml) for 30 minutes. It was then shown (nmr) that the reaction was complete and so the solvent was removed under reduced pressure and the resulting oil was triturated with petroleum ether (bp.40-60°). No crystalline product could be obtained, despite the indications (nmr) that o-dithiin, 69e, had formed.

δ,ppm ($CDCl_3$):	7.15 (m, C_6H_4)
	4.41,4.25(d,H-3,H-4,J=5.0Hz)
	3.95, 3.68 (s,CO_2CH_3)
	3.80, 3.75 (s,$-OCH_3$)

(Procedures A and C were also utilised for this reaction. In each case, nmr spectroscopy indicated that o-dithiin, 69e, had formed; however, the product could not be crystallised, even after column or preparative thin-layer chromatography.)

Dimethyl 3,4-dihydro-3,6-diphenyl-o-dithiin-4,5-dicarboxylate (161a)

i. (Procedure B)

Dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a; 0.39g, 1.0mmol) was heated under reflux in o-dichlorobenzene for 1½ hours after which time the reaction was shown (nmr) to be complete. Evaporation of the solvent in vacuo yielded a yellow oil (0.37g) which, after purification (preparative thin-layer chromatography), appeared to be pure but failed to give a crystalline product.

ii. (Procedure A)

The m-dithiin, 76a (0.39g, 1.0mmol), was heated at 185° under a nitrogen atmosphere for 1 hour during which time all of the starting material was consumed. The brown residue, on cooling, crystallised from methanol to give o-dithiin, 161a, as pale green prisms (0.17g, 43%) having mp.75-76°. (Found: C,62.1; H,4.6; S,16.6. $C_{20}H_{18}O_4S_2$ requires C,62.2; H,4.7; S,16.6%), ^{M}/e 386.

δ ,ppm ($CDCl_3$):	7.34 (s,C_6H_5)	
	5.05,4.65(d,H-3,H-4,J=4.0Hz)	
	3.72,3.39 (s,CO_2CH_3)	
ν max,cm^{-1}(KBr):	1749,1736(CO_2Me;C-4)	
	1690(CO_2Me;C-5)	
(nujol):	1750,1740(CO_2Me;C-4)	
	1690(CO_2Me;C-5)	
λ max,nm; MeOH:	220(ε13900),258*(ε6800)	
	323* (ε1800)	

*very weak absorption

A second product was isolated from the methanolic mother liquors and identified (microanalysis, ir, nmr and mass spectrometry) as dimethyl 2,5-diphenythiophen-3,4-dicarboxylate (97; 0.03g, 9%); mp.152° (lit.[193] 167°).

The above rearrangement was also attempted using Procedure C, but the reaction did not proceed cleanly, and a mixture was obtained after prolonged heating.

Dimethyl 4-deutero-3,4-dihydro-3,6-diphenyl-o-dithiin,4,5-dicarboxylate (161b)

(Procedure A)

Dimethyl 6-deutero-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76b; 0.39g, 1.0mmol) was heated at 185° under nitrogen for 1 hour, then allowed to cool. The residue was dissolved in methanol from which o-dithiin, 161b, crystallised as colourless prisms (0.18g, 47%) and had mp.84°, M/e 387.

δ ,ppm ($CDCl_3$)	7.20 (s,C_6H_5)
	4.91 (s,H-3)
	3.65, 3.28 (s,CO_2CH_3)

Attempted thermal rearrangement of 6-methyl m-dithiin, 76c

i. (Procedure B)

A solution of dimethyl 6-methyl-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76c; 0.4g, 1.0mmol) in o dichlorobenzene (5 ml) was heated under reflux and the reaction monitored (nmr) at regular intervals. The mixture which began to form after 30 minutes became gradually more complex as time progressed, and after 45 minutes many components were present.

ii. (Procedure A)

Samples of 6-methyl m-dithiin, 76c, were heated for 30 minutes at temperatures of 150°, 160°and 170° respectively and the residues were analysed by nmr spectroscopy. It was found that in those experiments carried out at temperatures of 150° and 160°, only unchanged starting material was present, whilst in the experiment conducted at 170°, a mixture was present which contained neither starting material nor o-dithiin. The mixture was shown (thin-layer chromatography) to contain at least 3 components.

10. Rearrangement of m- to o-Dithiins: Evidence for the Proposed Mechanism

Treatment of m-dithiins with radical initiators and scavengers under thermal rearrangement conditions

a. 1,1-Azobisisobutyronitrile (AIBN)

A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in toluene (30 ml) was heated for 7 hours under reflux in the presence of AIBN (0.02g, 0.1mmol). Clean conversion to o-dithiin, 69, occurred after this period, and when the AIBN was omitted an identical result was obtained.

b. Benzoyl Peroxide

m-Dithiin, 70a (0.39g, 1.0mmol), in toluene (30 ml) was heated under reflux in the presence of benzoyl peroxide (0.025g, 0.1mmol). Again, clean conversion of m- to o-dithiin occurred after about 7 hours' reflux indicating that the initiator had played no part in the reaction.

c. p-Benzoquinone

The above procedure was adopted with the inclusion of 5 equivalents of p-benzoquinone. This did not appear to retard the rearrangement to the o-dithiin in any way.

d. 2,2-Diphenyl-1-picrylhydrazyl (DPPH)

When m-dithiin 70a (0.39g, 1.0mmol) was refluxed in toluene (30 ml) containing DPPH (0.04g, 0.1mmol), the purple colour of the DPPH was not dissipated (as may have been expected if radicals were formed during the reaction). Instead, a moderate yield of o-dithiin, 69, was obtained

(0.19g, 49%).

Attempts to trap retro Diels-Alder intermediates in the thermal rearrangement of m-dithiins

a. Maleic anhydride

A mixture of maleic anhydride (0.49g, 5.0mmol) and dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in toluene (30 ml) was heated under reflux. Normal conversion to o-dithiin occurred with no side reactions. The same result was obtained in refluxing xylene.

b. Methyl propiolate

When the above procedure was followed using methyl propiolate (10 eq) as the competing dienophile, a mixture of o-dithiin 69 and unchanged starting material was obtained. Again, xylene was tried as solvent, but no adduct was formed.

c. Dimethyl acetylenedicarboxylate (DMAD)

m-Dithiin, 70a (0.39g, 1.0mmol), and DMAD (1.0g, 7.0mmol) were heated together under a nitrogen atmosphere at 195^{o} for 30 minutes and the reaction was monitored by thin-layer chromatography. A mixture of several components formed which contained neither o-dithiin, 69, nor unchanged m-dithiin.

The reaction was repeated using only 1 equivalent of DMAD. The resultant mixture, which was less complex than that previously obtained, was separated by preparative thin-layer chromatography. The main band was eluted and the solvent was evaporated under reduced pressure to give

a yellow oil (0.045g) which could not be crystallised. This was identified by nmr and mass spectroscopic analysis as tetramethyl 2-phenyl-2H-thiopyran-3,4,5,6-tetracarboxylate (163), $^{M}/e$ 406.

δ ,ppm($CDCl_3$): 7.25 (m,C_6H_5)
4.74* (s,H-2)
3,84,3.82,3.47,3.37
(s, 4 x CO_2CH_3)

A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in xylene (30 ml) was heated under reflux for 3 hours with DMAD (0.43g, 3.0mmol). Thin-layer chromatography indicated that some thermal rearrangement had taken place yielding o-dithiin, 69, but also that a new, more polar component had formed. The new component was separated from the mixture by preparative thin-layer chromatography, and isolated as a yellow oil (0.055g) which did not crystallise. The product was identified (nmr, mass spectroscopy) as the symmetrical adduct, tetramethyl 4-phenyl-4H-thiopyran-2,3,5,6-tetracarboxylate (164), $^{M}/e$ 406.

δ ,ppm($CDCl_3$): 7.30 (s,C_6H_5)
5.15 (s,H-4)
3.83 (s, 2 x CO_2CH_3)
3.71 (s, 2 x CO_2CH_3)

* c.f. H-4 shift of 4.78 ppm in m-dithiin 70a (starting material)

Isomerisation of dimethyl cis-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69a)

a. Cis o-dithiin, 69a (0.02g, 0.05mmol), was dissolved in deutero-chloroform (0.7 ml) and placed in a nmr tube. The nmr spectrum was recorded, then DABCO (0.012g, 0.1mmol) was added. The nmr spectrum of the mixture became gradually more complex over a 2 hour period, and no trans o-dithiin isomer, 69, was observed after the sample had been washed with dilute hydrochloric acid.

A similar result was obtained when triethylamine was used instead of DABCO.

b. Cis o-dithiin, 69a (0.04g, 0.1mmol), was dissolved in o-dichlorobenzene (0.7 ml) and placed in a nmr tube. The nmr from the sample was recorded at room temperature then the temperature in the probe was increased stepwise, a spectrum being recorded after each increase. No change was observed for temperatures below 160°; at 170°, the AB quartet due to the coupling methine ring protons collapsed, and within a few minutes a new quartet had formed. The two ester methyl absorptions began to disappear and were replaced with new peaks having slightly different chemical shifts (see Table 5, page 116). At 175° the new spectrum was completely established. The sample was allowed to cool to room temperature, then its spectrum was compared with that of a genuine sample of trans o-dithiin, 69; the two spectra were identical. The sample was diluted with petroleum ether (bp. 40-60°, 2 ml) from which trans o-dithiin, 69 crystallised overnight as pale green cubes (0.04g, 100%);

mp.113°.

c. Two samples of cis o-dithiin, 69a, were heated under reflux in xylene (4 hours) and toluene (8 hours) respectively. A quantitative yield of trans o-dithiin, 69, was obtained in each case.

11. Attempted Deprotonation of o-Dithiins

Treatment with n-butyllithium

A solution of dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) in dry THF (40 ml) was cooled to -78° and stirred under nitrogen. A 1.6 molar hexane solution of n-butyllithium (0.63 ml, 1.0mmol) was added dropwise and the temperature was maintained below -50° for 1 hour. The reaction mixture was then divided into two equal portions, one being quenched with excess deuterium oxide (2 ml) and the other with dilute hydrochloric acid (2 ml). Both fractions were stirred overnight at room temperature, and after work-up (which involved evaporation of solvent *in vacuo* and water washes), they were shown (nmr) to be identical mixtures. There were indications in the nmr spectra that some S-butylation had occurred, although a sample of unchanged starting material was obtained after preparative thin-layer chromatography.

Treatment with n-butyllithium - DABCO

The above experiment was repeated 3 times with the inclusion of DABCO (0.11g, 1.0mmol) at temperatures of -50°, -20° and 20° respectively. Each reaction mixture was worked-up as previously to give a mixture which contained unchanged o-dithiin together with (what appeared from the nmr spectrum) S-butylated material. Unchanged starting material was the major product at -50°, whereas at 20°, little

starting material was present; no deuteration was observed in any of the three cases.

Treatment with lithium diisopropylamide

Lithium diisopropylamide (1.0mmol) was prepared by the additon of a 1.6 molar hexane solution of n-butyllithium (0.625 ml, 1.0mmol) to diisopropylamine (0.1 g, 1.0mmol). This was added dropwise to a stirred solution of o-dithiin, 69 (0.39g, 1.0mmol), in dry THF under nitrogen at -15° and the resulting blue solution was stirred for 1 hour then allowed to warm to room temperature. An excess of deuterium oxide (2 ml) was used to quench the reaction and after stirring overnight this was processed as described above. The resultant yellow oil was shown (nmr) to consist mainly of unchanged starting material.

Attempted phase-transfer deprotonation of o-dithiin 69

Dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) in dry benzene (30 ml) was heated under reflux with anhydrous potassium carbonate (1.38 g, 10mmol) and benzyl tri-n-butylammonium bromide (BTBAB; 0.36 g, 1.0mmol). The reaction was monitored at regular intervals by thin-layer chromatography and after 6 hours the rate of disappearance of starting material was very low. The mixture was cooled, filtered, washed with dilute hydrochloric acid and extracted with saturated sodium bicarbonate. The extracts were combined, acidified and re-extracted with dichloromethane to give a brown solution. This was concentrated in vacuo, affording an oil (0.1 g) which could not be crystallised; nmr

spectroscopic analysis indicated that this was extremely impure. The bicarbonate-insoluble fraction was shown (nmr) to be unchanged starting material.

Attempted phase-transfer methylation of o-dithiin, 69

A mixture of o-dithiin, 69 (0.39 g, 1.0mmol), benzyl triethylammonium chloride (BTEAC; 0.1 g, 0.5mmol) and anhydrous potassium carbonate (0.69 g, 5mmol) in dichloromethane (15 ml) was stirred vigorously at room temperature. A yellow colour had developed after 30 minutes and methyl iodide (0.71 g, 5mmol) was added. A very slow reaction followed, and a brightly fluorescent uv active component was formed over a period of 12 hours. This was isolated (after preparative thin-layer chromatography) as colourless needles and identified by ir and mass spectroscopy as dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91; 0.04g, 21%), mp.92° (lit.[133] 85°).

12. Attempted Dehydrogenation of o-Dithiins

a. 3,4,5,6-Tetrachloro-1,2-benzoquinone (o-chloranil)

Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) and o-chloranil (0.25g, 1.0mmol) were heated under reflux in xylene (20 ml) for 15 hours. No reaction had occurred after this period, and 90% of the starting material was recovered.

b. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

A solution of o-dithiin, 69, was treated with 1 equivalent of DDQ using the above procedure, and an identical result was obtained.

c. Trityl fluoroborate

Trityl fluoroborate (0.39g, 1.2mmol) was added to a solution of o-dithiin, 69 (0.39g, 1.0mmol), in acetonitrile (30 mls). The mixture was heated under reflux for 15 hours during which time no reaction had occurred.

When the reaction was repeated using glacial acetic acid as the solvent, a mixture formed during 22 hours heating under reflux. Evaporation of solvent *in vacuo* gave a brown oil which was shown (by reaction with 2,4-dinitrophenylhydrazine) to contain benzaldehyde; no trace of a dehydrogenated o-dithiin was detected.

Attempted bromination of o-dithiin, 69

a. n-Bromosuccinimide (NBS)

Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) was

dissolved in dry (ethanol-free) chloroform (20 ml) and NBS (0.4g, 2.5mmol) was added. The solution was heated under reflux for 3 hours, after which time thin-layer chromatography indicated that a new component was forming. A further 2.5 equivalents of NBS were added, but this did not appear to produce any significant increase in the consumption of starting material over a 7 hour period. The solvent was evaporated under reduced pressure to give a brown oil, which, after purification (preparative thin-layer chromatography), afforded dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91; 0.09g, 24%); mp.92° (lit.[133] 85°).

b. n-Bromosuccinimide - 1,1'-azobisisobutyronitrile

A solution of o-dithiin, 69 (0.39g, 1.0mmol), and AIBN (0.02g, 0.1mmol) in dry carbon tetrachloride (30 ml) was heated under reflux. NBS (0.8g, 5.0mmol) was added and after refluxing for 10 hours, it was shown (nmr) that the only new product formed was the same thiophen (91) which had been isolated in the preceding experiment.

This was repeated using benzene as the solvent, but again, thiophen 91 was the only product isolated.

13. General Methods for Desulphurisation of o-Dithiins

A. Triphenylphosphine

The o-dithiin (1 eq.) was dissolved in dichloromethane and the solution was stirred magnetically at room temperature. Triphenylphosphine (1 eq.) was added over a period of 5 minutes, and the reaction mixture was allowed to stand for 18 hours when it was shown by thin-layer chromatography to be complete. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel; Brockmann grade II, dichloromethane), yielding the pure product as colourless needles. (In certain specified cases, this procedure was modified by the use of D_6 acetone as the solvent, in order to allow the experiment to be monitored by nmr spectroscopy.)

B. Hexamethylphosphorous triamide

A solution of o-dithiin (1 eq.) in dichloromethane was stirred magnetically at 0^{o} under nitrogen.

Hexamethylphosphorous triamide (1 eq.) was added dropwise over a period of 5 minutes, and the solution was allowed to warm slowly to room temperature. The next day, it was shown by thin-layer chromatography that the reaction had gone to completion and so the solution was concentrated in vacuo (to approximately 2 ml) and purified by passage through a silica gel column (Brockmann grade IV, dichloromethane:petroleum ether (bp. 40-60^{o})/80:20). Evaporation of solvent gave a yellow

oil which crystallised on trituration with petroleum ether (bp. 40-60°).

The following 2,3-dihydrothiophens were prepared according to procedure A, which utilises triphenylphosphine. (Procedure B although equally efficient, involves the formation of the sulphur analogue of hexamethylphosphoric triamide (HMPA) as a byproduct; this is highly toxic, and thus the procedure was less attractive for routine use.)

Dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169)

Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) and triphenylphosphine (0.26g, 1.0mmol) were dissolved in dichloromethane (20 ml). The product, 169 (0.34g, 95%), was isolated as colourless needles after chromatography, and had mp. 150-152°. (Found: C,67.2; H,5.1. $C_{20}H_{18}O_4S$ requires C; 67.8; H,5.1%), $^M/e$ 354.

δ, ppm($CDCl_3$):	7.05 (m, C_6H_5)
	5.60,4.50(d,H-2,H-3,J=9.0Hz)
	3.90,3.56(s,CO_2CH_3)
ν max, cm^{-1}:	1742, 1711 (CO_2Me)

This compound was also prepared in 85% yield using Procedure B.

Dimethyl trans-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169a)

Cis o-dithiin, 69a (0.04g, 1.0mmol), in D_6 acetone (0.7ml) was treated with triphenylphosphine (0.035g, 0.1mmol) and the solution was placed in a nmr tube. The

reaction was shown by nmr to be complete after 20 hours at room temperature, and the title compound, 169a (0.03g, 92%), was isolated as colourless needles (mp. 63-65°) after preparative thin-layer chromatography. (Found: C,67.7; H,5.3. $C_{20}H_{18}O_4S$ requires C,67.8; H,5.1%), $^M/_e$ 354.

δ ,ppm($CDCl_3$): 7.33(s,C_6H_5)
4.68,4.67(d,H-2,H-3,J= <1Hz)
3.90,3.57(s,CO_2CH_3)

ν max,cm^{-1}: 1735, 1700 (CO_2Me)

Dimethyl 2,3-di-p-chlorophenyl-2,3-dihydrothiophen-4,5-dicarboxylate (169c)

Dimethyl 3,4-di-p-chlorophenyl-3,4-dihydro-o-dithiin-5,6-dicarboxylate (69c; 0.46g, 1.0mmol) was dissolved in dichloromethane (20 ml) and triphenylphosphine was added. The reaction was complete after 2 days, and the dihydrothiophen diester, 169c (0.3g, 71%), was obtained as colourless needles having mp. 158°. (Found: C,56.3; H,3.9. $C_{20}H_{16}Cl_2O_4S$ requires C,56.7; H,3.8%.)

δ ,ppm($CDCl_3$): 6.9(m,C_6H_4)
5.49,4.47(d,H-2,H-3,J=8.5Hz)
3.88,3.56(s,CO_2CH_3)

Methyl 2,3-dihydro-2,3-diphenylthiophen-4-carboxylate (169b)

A solution of methyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5-carboxylate (69b; 0.33g, 1.0mmol) in ethanol (20 ml) containing triphenylphosphine (0.52g, 2.0mmol) was heated under reflux for 10 hours. The solvent was evaporated under reduced pressure, affording a yellow oil which was purified by preparative thin-layer chromatography.

The product, 169b (0.15g, 51%), crystallised as colourless needles from methanol and had mp. 164°. (Found: C,71.5; H,5.4; $C_{18}H_{16}O_2S$ requires C.73.0; H,5.4%), ^{M}/e 296.

δ ,ppm($CDCl_3$):	7.70(s,H-5)
	6.97(m,C_6H_5)
	5.52,4.36(d,H-2,H-3,J=8.0Hz)
	3.58(s,CO_2CH_3)
ν max,cm^{-1}:	1705 (CO_2Me)

Dimethyl 2,3-dihydro-2,5-diphenylthiophen-3,4-dicarboxylate (170)

Triphenylphosphine (0.26g. 1.0mmol) was added to a solution of dimethyl 3,4-dihydro-3,6-diphenyl-o-dithiin-4,5-dicarboxylate (161a; 0.18g, 0.5mmol) in acetone (4 ml). The reaction was shown (nmr) to be complete after 8 days at room temperature, and after the usual work-up (involving preparative thin-layer chromatography), the title compound, 170, crystallised as colourless needles (0.15g, 88%) and had mp. 109-110°. (Found: C,67.4; H,5.0. $C_{20}H_{18}O_4S$ requires C,67.8; H,5.1%), ^{M}/e 354.

δ ,ppm($CDCl_3$):	7.45(d,C_6H_5,J=2Hz)
	5.32,4.58(d,H-2,H-3,J=10.5Hz)
	3.52,3.25(s,CO_2CH_3)
ν max,cm^{-1}(KBr):	1725 (CO_2Me)
(nujol):	1725 (")

14. Dehydrogenation of 2,3-Dihydrothiophens

Treatment of cis 2,3-dihydrothiophen, 169, with DDQ

A solution of dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169; 0.04g, 0.1mmol) in deutero-chloroform (1.0 ml) was treated with DDQ (0.05g, 0.15mmol). The reaction mixture was heated for 1 hour under reflux, during which time a fine precipitate formed; this was removed by filtration and discarded. The solvent was evaporated in vacuo and the product was isolated by preparative thin-layer chromatography, appearing under uv light as a bright fluorescent band. Dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91; 0.03g, 89%) was purified by distillation under reduced pressure (0.1 mm Hg, oil bath temperature 120°) and had mp. 92° (lit.[133] 85°). (Found: C,68.0; H,4.5. calculated for $C_{20}H_{16}O_4S$, C,68.2; H,4.6%). $^M/_e$ 352.

δ,ppm($CDCl_3$):	7.24(s,C_6H_5)
	3.89,3.73(s,CO_2CH_3)
νmax,cm^{-1}:	1736,1725 (CO_2Me)

A sample of the above thiopen (91) was prepared independently using the method of Schrauzer and Mayweg[133]. (This involved the reaction of benzoin with phosphorus pentasulphide, followed by nickel (II) chloride hexahydrate to give an intermediate nickel complex (which was isolated). This in turn, reacted with DMAD at 90° to give a p-dithiin which spontaneously extruded sulphur affording the product, 91, in 28% overall yield; mp. 91° after purification.)

Treatment of trans 2,3-dihydrothiophen, 169a with DDQ

DDQ (0.045g, 0.15mmol) was added to a solution of dimethyl trans-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169a; 0.04g, 0.1mmol) in chlorobenzene (1.5 ml). The reaction mixture was heated under reflux for 12 hours and the fine precipitate which had formed during this time was filtered and discarded. Dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91) was isolated as colourless prisms (0.035g, 94%) after purification by distillation and had mp. 92-93° (lit.[133] 85°).

Treatment of dimethyl 2,3-dihydro-2,5-diphenylthiophen-3,4-dicarboxylate (170) with DDQ

A solution of 2,3-dihydrothiophen, 170 (0.04g, 0.1mmol), in deutero-chloroform was treated with DDQ (0.05g, 0.2mmol). A fine precipitate had formed after 1 hour at room temperature; this was filtered and discarded. The residue was purified by preparative thin-layer chromatography, yielding dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97; 0.03g, 88%) as colourless needles. The product was recrystallised from methanol and had mp. 152° (lit.[193] 167°). The identity of the product was confirmed by mixed melting point, nmr and mass spectroscopy (^{M}/e 352).

Treatment of dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169) with n-butyllithium

The 2,3-dihydrothiophen, 169 (0.35g, 1.0mmol), was treated with 1.6 molar n-butyllithium (0.63 ml, 1.0mmol) at -50° under nitrogen in the way described (page158) for

m-dithiins. It was shown subsequently by thin-layer chromatography and nmr spectroscopy that a mixture containing many components (including unchanged starting material) was present; the mixture was too complex to merit separation.

When the experiment was repeated with the inclusion of 1 equivalent of DABCO, no advantage was afforded and an equally complex mixture was obtained.

15. Tests for Disulphide Linkage in o-Dithiins

a. Sodium Nitroprusside

The o-dithiin (0.1mmol) was dissolved, with warming, in methanol (2 ml) and sodium borohydride (10mmol) was added. When the vigorous evolution of gas had ceased, the solution was treated with a saturated solution of sodium nitroprusside (1 ml). The appearance of a transient violet colour indicated a positive test.

b. Lead (II) acetate

The o-dithiin was treated with sodium borohydride as described above. The solution was made slightly acidic by the dropwise addition of acetic acid, then shaken with a saturated solution of lead (II) acetate in methanol (1 ml). A yellow precipitate indicated a positive test.

The following compounds gave positive results in the above tests:

- Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69)
- Dimethyl cis-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69a)
- Dimethyl 3,4-dihydro-3,6-diphenyl-o-dithiin-4,5-dicarboxylate (161a).

The following compounds gave negative tests:

- Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)
- Dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169).

16. Oxidation of o-Dithiins

General procedure

A stirred solution of the o-dithiin in dichloromethane was treated with 85% MCPBA (1.2 eq.) and the reaction was monitored by thin-layer chromatography. When the reaction was complete, the solution was washed repeatedly with saturated sodium bicarbonate, with water, and was dried ($MgSO_4$). Evaporation of solvent in vacuo gave a yellow oil which crystallised on treatment with methanol. The product was purified by recrystallisation from methanol.

The following sulphoxides were prepared as outlined above:

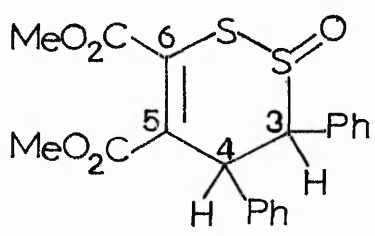
Trans-5,6-Dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide (172)

Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) was dissolved in dichloromethane (20 ml) and the solution was treated with 85% MCPBA (0.24g, 1.2mmol). The reaction was complete after 1 hour, and the product, 172, crystallised as colourless prisms (0.16g, 61%) having mp. 140°. (Found: C,59.6; H,4.5. $C_{20}H_{18}O_5S_2$ requires C,59.7; H,4.5%), $^M/e$ 402.

^{1}Hnmr, δ, ppm, ($CDCl_3$): 7.16(d,C_6H_5,J=9.0Hz)
4.83,4.47(d,H-3,H-4, J=12.0Hz)
3.80, 3.42 (s,CO_2CH_3)

ν max, cm^{-1}: 1732, 1722 (CO_2Me)

^{13}Cnmr, δ, ppm($CDCl_3$): 137.2(C-6 or C-5)
135.5(C-5 or C-6)
71.1(C-3)
44.5(C-4)



(172)

Cis-5,6-dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide (172a)

A solution of cis o-dithiin, 69a (0.04g, 0.1mmol), in deutero-chloroform (0.7 ml) was treated with 85% MCPBA (0.024g, 0.12mmol) and the solution was placed in a nmr tube. The reaction was shown (nmr) to be complete after 1 hour, and the sulphoxide, 172a, crystallised from ether as colourless prisms (0.015g, 37%); mp. 132°, M/e 402.

δ, ppm($CDCl_3$): 7.20 (m,C_6H_5)
5.17,4.33(d,H-3,H-4, J=2.0Hz)
3.89,3.48(s,CO_2CH_3)

ν max, cm^{-1}: 1738, 1721 (CO_2Me)

Attempted preparation of 4,5-dimethoxycarbonyl-3,4-dihydro-3,6-diphenyl-o-dithiin-2-oxide (173)

A solution of dimethyl 3,4-dihydro-3,6-diphenyl-o-dithiin-4,5-dicarboxylate (161a; 0.04g, 0.1mmol) in deutero-chloroform was treated with 1.2 equivalents of MCPBA and the reaction was monitored by nmr spectroscopy. All starting material had been consumed and a mixture had

formed after 1½ hours; work-up as previously, afforded a crystalline product which was identified (nmr, ir and mixed melting point) as dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97; 0.02g, 48%); mp. 149-150° (lit.[193] 167°). The remaining components of the mixture could not be isolated.

17. Reactions of m- and o-Dithiin Sulphoxides

A. Further oxidation

a. m-Chloroperbenzoic acid (MCPBA)

A stirred solution of 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b; 0.4g, 1.0mmol) in dichloromethane was treated with 85% MCPBA (0.24g, 1.2mmol). A mixture containing at least 5 components (including starting material) had formed after 1 hour; this did not change on standing for 20 hours at room temperature. Benzaldehyde was detected by smell, and its identity confirmed by comparison (using thin-layer chromatography and 2,4-dinitrophenylhydrazine spray) with an authentic sample. None of the main components of the mixture was more polar than the starting material (as would have been expected for the disulphoxide or sulphone) and a similar mixture was formed when a large excess of MCPBA was used.

Trans-5,6-dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide (172) was treated with 1.2 equivalents of MCPBA in the way described above. Again, a mixture which contained 4 or 5 components was formed; none of these was more polar than the starting material.

b. Hydrogen peroxide

A solution of 5,6-dimethyoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b; 0.4g, 1.0mmol) in glacial acetic acid (50 ml) was treated with 50% hydrogen peroxide (0.14g, 2.0mmol) at 0^{o}. It was found after 1 hour that ring opening was occurring, as evidenced by the detection of benzaldehyde.

c. Sodium periodate

A solution of trans o-dithiin-2-oxide, 172 (0.4g, 1.0mmol), in isopropanol (30 ml) was stirred and heated at 60°. An aqueous solution of sodium periodate (0.23g, 1.1mmol) was added, followed by a single crystal of elemental iodine. No reaction was observed after 10 hours, and an identical result was obtained with acetonitrile as the solvent.

B. Pyrolysis

5,6-Dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b; 0.04g, 1.0mmol) was heated in a nmr tube at 150°. On melting (144°), the sample began to evolve gas; this continued for 20 minutes, after which time it was shown (nmr, thin-layer chromatography) that a complex mixture had formed; no unchanged starting material was present. One of the major components was identified as dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91).

An equally complex mixture was formed when trans o-dithiin-2-oxide, 172, was heated at 145° for 10 minutes. None of the components could be isolated.

C. Treatment with n-butyllithium

A solution of 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b; 0.4g, 1.0mmol) in dry THF (25 ml) was treated with 1 equivalent of n-butyllithium at -78° using the procedure adopted (page 158) for the lithiation of m-dithiins. The orange/red solution was quenched with deuterium oxide (2 ml), and after the normal work-up procedure, a brown oil was produced. This

was shown to be a 3-component mixture (no starting material remained) and the main component was isolated by preparative thin-layer chromatography. Dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91) was identified by nmr and mass spectroscopy and crystallised as colourless needles on treatment with methanol (0.12g, 34%); mp. 91° (lit.[133] 85°).

Trans-5,6-dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide (172; 0.4g, 1.0mmol) was treated with 1 equivalent of n-butyllithium at 78° using the above procedure. Nmr spectroscopic analysis of the crude residue indicated the likely presence of acyclic S-butyl components (evidenced by a comparison of methine proton coupling constants with diphenylethanes).

D. Treatment with acids (m-dithiin sulphoxide only)

5,6-Dimethoxycarbonyl-2,4-diphenyl-4H-m-dithiin-3-oxide (87b; 0.4g, 1.0mmol) was dissolved in acetonitrile (30 ml) and concentrated hydrochloric acid (0.5 ml) was added. All starting material had been consumed after 24 hours and a multicomponent mixture had formed. The volume of the solution was reduced in vacuo to 5 ml, diluted with dichloromethane (25 ml), and washed repeatedly with water. The solution smelled strongly of benzaldehyde, and its presence was confirmed by thin-layer chromatography using a 2,4-dinitrophenylhydrazine spray. A pure sample of the expected byproduct, dimethyl 3-phenyldithiole-4,5-dicarboxylate (93) could not be obtained due to poor chromatographic resolution.

An identical result was obtained when perchloric

acid was used in place of hydrochloric acid, but when hydrogen chloride gas or boron trifluoride etherate was used, no reaction was observed.

E. Treatment with acetic anhydride

i. A solution of 5,6-dimethoxycarbonyl-2,4-diphenyl-4H-*m*-dithiin-3-oxide (87b; 0.4g, 1.0mmol) in benzene (20 ml) was treated with freshly distilled acetic anhydride (0.2g, 2.0mmol) and the solution was refluxed for 12 hours. The solution was washed repeatedly with water, and extracted twice with saturated sodium bicarbonate. Evaporation of solvent *in vacuo* gave an oil from which unchanged starting material crystallised (0.34g, 85%) on treatment with methanol.

Trans *o*-dithiin-2-oxide, 172, also failed to react under identical conditions.

ii. *m*-Dithiin-3-oxide, 87b (0.4g, 1.0mmol), was dissolved in acetic anhydride (30 ml) and the solution was heated at 100° for 4 hours. Thin-layer chromatography after this period indicated that a mixture containing 4 new components was present; this was separated on preparative thin-layer plates, and the main two bands were eluted. These were shown (nmr; mass spectroscopy) to be stilbene (0.07g) and dimethyl 3,4-dihydro-3,4-diphenyl-*o*-dithiin-5,6-dicarboxylate (69; 0.08g) respectively.

When *trans* *o*-dithiin-2-oxide, 172, was treated with acetic anhydride in the way described above,

an even more complex mixture formed (6 hours). Attempts were made to purify this by preparative thin-layer and column chromatography, but these were unsuccessful.

F. Attempted α-halogenation (o-dithiin sulphoxide only)

i. Sulphuryl chloride

A solution of trans-5,6-dimethoxycarbonyl-3,4-dihydro-3,4-diphenyl-o-dithiin-2-oxide (172; 0.4g, 1.0mmol) in dichloromethane (25 ml) was treated with sulphuryl chloride (0.27g, 2.0mmol). All starting material was consumed after 1 hour and a 3 component mixture had formed. The solution was washed repeatedly with water, was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The resultant yellow oil could not be crystallised, and was purified by preparative thin-layer chromatography.

The two main components were identified; (nmr; mass spectroscopy) these were dimethyl 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.08g) and dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91; 0.12g). No chlorinated product was detected.

ii. Bromine-pyridine

A solution of trans o-dithiin-2-oxide, 172 (0.4g, 1.0mmol), in dry THF (20 ml) was treated with pyridine (2.5g, 30mmol) and silver nitrate (0.41g, 2.5mmol). The mixture was cooled to -60° under nitrogen and bromine (0.08 ml, 1.5mmol) was added

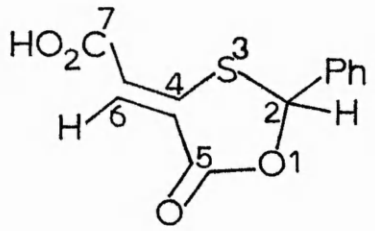
dropwise. Stirring was continued for 2 hours then the reaction mixture was allowed to warm slowly to room temperature. All starting material had been consumed and so the inorganic salts were removed by filtration and the solution was partitioned between water and dichloromethane. The organic fraction was washed with saturated sodium thiosulphate, dilute sulphuric acid, water, and was dried ($MgSO_4$). Following evaporation of the solvent *in vacuo*, the residue was purified by dry column chromatography (silica gel; Brockmann grade II - dichloromethane), giving a yellow oil (0.04g), the nmr spectrum of which showed the loss of a methine proton. The mass spectrum did not show a molecular ion, but revealed that bromine had *not* been incorporated into the molecule.

18. Reaction of Acetylenedicarboxylic Acid with 2,4,6-Triphenyl-1,3,5-Trithiane

2,4,6-Triphenyl-1,3,5-trithiane (0.37g, 1.0mmol) was dissolved in dry, refluxing acetonitrile (20 ml) and boron trifluoride etherate (1 ml) was added. A purple colour was observed after 10 minutes and a solution of acetylenedicarboxylic acid (0.23g, 2.0mmol) in dry acetonitrile (10 ml) was added dropwise over a period of 30 minutes. The trithiane had been consumed after 3 hours, and the mixture was allowed to cool then partitioned between water and ether. The organic fraction was extracted with saturated sodium bicarbonate and the combined aqueous extracts were acidified, extracted with dichloromethane and the organic extract was dried ($MgSO_4$). Evaporation of solvent under reduced pressure gave a yellow oil, which was extracted with petroleum ether (bp. 80-100°) using a Soxhlet apparatus. The product crystallised from the petroleum ether on cooling as pale yellow plates and had mp. 154-156°. This was purified by recrystallisation from aqueous methanol, and was identified (^{13}C and ^{1}Hnmr, ir and mass spectroscopy) as the lactone, 5-oxo-2-phenyl-1,3-oxathiolylidene acetic acid (99; 1.1g, 23%). (Found: C,55.7; H,3.3: S,13.6; $C_{11}H_8O_4S$ requires C,55.9; H,3.4; S,13.6%), ^{M}/e 236.

^{1}Hnmr, δ, ppm($CDCl_3/D_6DMSO$): 10.4 (s, $CO_2\underline{H}$)
7.39 (s, C_6H_5)
6.82 (s, = CH)
6.51 (s, H-2)

^{13}Cnmr, δ, ppm		
DMSO	DMSO -Et_3N	assignment (see diagram)
80.83	80.01	C-2
115.72	126.06	C-6
141.34	132.56	C-4
166.64	167.88	C-7(or C-5)
166.96	168.91	C-5(or C-7)



(99)

Ir data for 99 are given in Appendix B.

19. Preparation and Reaction of 'Acid-Protected' Acetylenedicarboxylates

Attempted preparation of di-t-butyl acetylenedicarboxylate

Concentrated sulphuric acid (1 ml) was added slowly, with stirring, to t-butyl alcohol (1.48g, 20mmol) and the temperature was maintained below 30°. The monopotassium salt of acetylenedicarboxylic acid (1.52g, 10mmol) was added, and stirring was continued for 4 days. No reaction had occurred after this period. The reaction mixture was heated at 80° for several hours, but still, no esterification had taken place.

Bis-2,2,2-trichloroethyl acetylenedicarboxylate (102)

(An unsuccessful attempt to prepare this compound was made using N-methyl pyridinium iodide as a coupling agent[195].)

A solution of acetylenedicarboxylic acid (1.14g, 10mmol) in 2,2,2-trichloroethanol (10 ml, 200mmol) was stirred at 55-60°. Boron trifluoride etherate was added dropwise, and heating was continued for 60 hours. Most of the 2,2,2-trichloroethanol was then removed *in vacuo*, and the oily residue was purified by column chromatography (toluene:ethyl acetate/80:20). The title compound, 102, crystallised as colourless needles (1.32g, 35%) from petroleum ether (bp. 60-80°) and had mp. 69-72°. (Found: C,25.7; H,1.1; Cl,55.6. $C_8H_4Cl_6O_4$ requires C,25.5; H,1.1; Cl,56.5%), $^M/_e$ 374.

δ ,ppm($CDCl_3$):	4.94 (s,$C\underline{H}_2CCl_3$)
ν max, cm^{-1}:	1748 ($CO_2CH_2CCl_3$)

Bistrimethylsilyl acetylenedicarboxylate (101)

(Two unsuccessful attempts were made to prepare this diester using first, trimethylsilyl chloride-pyridine, then trimethylsilyl chloride under phase-transfer conditions.)

Acetylenedicarboxylic acid (1.14g, 10mmol) and N-trimethylsilyl acetamide (2.64g, 20mmol) were suspended in carbon tetrachloride (40 ml). The mixture was heated under reflux for 3 hours, during which time the N-trimethylsilyl acetamide dissolved, but the acid remained on the surface in a molten state. The solution was cooled, and colourless crystals of acetamide separated and were filtered off. The solvent was evaporated *in vacuo*, and the product, 101, distilled (0.1 mm Hg, 76°) as a colourless oil (0.1g, 39%) crystallising as colourless needles when cooled below 15°. Microanalysis was impossible due to decomposition; $^{M}/_{e}$ 258.

ν max, cm^{-1}: 1723 (CO_2SiMe_3)

Reaction of Bis-2,2,2-trichloroethyl acetylenedicarboxylate (102) with 2,4,6-triphenyl-1,3,5-trithiane

2,4,6-Triphenyl-1,3,5-trithiane (0.24g, 0.65mmol) was dissolved in dry toluene (30 ml) at 85°, and boron trifluoride etherate (1 ml) was added. A solution of the acetylenic ester, 102 (0.37g, 1.0mmol), in toluene (10 ml) was added dropwise over a period of 25 minutes, and it was found (thin-layer chromatography) that no reaction had occurred. A further equivalent of the acetylenic ester was added, but heating at 85° for 3 hours resulted in no *m*-dithiin formation. Unreacted trithiane crystallised

from the reaction mixture on cooling (0.2g).

Reaction of Bistrimethylsilyl acetylenedicarboxylate (101) with 2,4,6-triphenyl-1,3,5-trithiane

The trithiane (0.24g, 0.65mmol) was treated with the acetylenic ester, 101 (0.26g, 1.0mmol), in the way described above; the only reaction which occurred was the decomposition of the bistrimethylsilyl ester. Unreacted trithiane (0.15 g) was again recovered from the cooled reaction mixture.

20. Attempted Hydrolysis of *m*- and *o*-Dithiins

A. Treatment with hydroxide ion

a. Aqueous potassium hydroxide-tetrahydrofuran

i. A stirred solution of dimethyl 2,4-diphenyl-4H-*m*-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in THF (30 ml) was treated with a solution of potassium hydroxide (0.15g, 2.7mmol) in water (2 ml). The reaction mixture was stirred at room temperature for 1 hour, during which time all starting material had been consumed. The orange coloured solution was acidified, and after the THF had been evaporated *in vacuo*, the residue was dissolved in dichloromethane, was washed repeatedly with water, then dried ($MgSO_4$). Analysis of the crude product (after removal of solvent) by nmr spectroscopy revealed that an extremely complex mixture was present; none of the residue dissolved in saturated sodium bicarbonate.

ii. When the 6H-tautomer, dimethyl 2,4-dipheny-6H-*m*-dithiin-5,6-dicarboxylate (76a) was reacted with potassium hydroxide using the above conditions, an equally complex mixture resulted.

iii. Dimethyl 6-methyl-2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76c), as expected, was slower to react with potassium hydroxide than

the two previous unsubstituted m-dithiins. No reaction was observed after 3 hours at room temperature, and so the solution was refluxed for 6 hours. The resultant foul smelling mixture could not be crystallised, and there was no evidence of any ester hydrolysis having taken place.

iv. Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69) was treated with potassium hydroxide as described for the above m-dithiins. An odorous brown oil was obtained after 1 hour at room temperature; this was a multicomponent mixture containing neither unchanged starting material nor any acidic product.

b. Aqueous potassium hydroxide-acetonitrile

i. A solution of dimethyl 2,4-diphenyl-4H-m-dithiin (70a; 0.39g, 1.0mmol) in acetonitrile (30 ml) was stirred with a solution of potassium hydroxide (0.15g, 2.7mmol) in water (2 ml). A mixture had formed after two hours at room temperature; the orange/red solution was acidified and the solvent was removed in vacuo. The residue was dissolved in dichloromethane, was washed with water then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to yield a brown oil which crystallised when treated with methanol. The product, dimethyl

2,5-diphenylthiophen-3,4-dicarboxylate (97) was purified by sublimation in vacuo (10mmHg, 195°) (0.19g, 55%) and had mp. 153° (lit.[193] 167°). (Found: C,68.4; H,4.6; calculated for $C_{20}H_{16}O_4S$; C,68.2; H,4.6%) M/e 352.

δ,ppm($CDCl_3$): 7.45(s,C_6H_5) (7.50)
3.75(s,CO_2CH_3) (3.78) lit.[193]

ν max,cm^{-1}: 1728 (CO_2Me)

ii. Dimethyl 6-methyl-2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76c) was treated with potassium hydroxide as described above. A multicomponent mixture resulted after 6 hours at room temperature and no thiophen was obtained.

c. Aqueous potassium hydroxide: phase-transfer conditions

i. A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dichloromethane was stirred vigorously with a 50% aqueous solution of potassium hydroxide. Benzyl triethylammonium chloride (BTEAC, 0.26g, 1.0mmol) was added and the colour of the mixture darkened immediately to deep red. Methyl iodide (2.0 ml, 15mmol) was added to the mixture after 10 minutes, and the colour lightened to pale yellow over a period of 20 minutes. The phases were separated and the organic layer was washed with dilute acid, water and was dried

($MgSO_4$). Evaporation of solvent *in vacuo* afforded a foul smelling oil which was shown (thin-layer chromatography) to contain at least 3 components. This crystallised, however, on treatment with methanol, and the product was identified as dimethyl 2,5-diphenylthiophen-3,4-dicarboxylate (97; 1.8g, 51%); mp. 152° (lit.[193] 167°).

ii. When dimethyl 2,4-diphenyl-6H-*m*-dithiin-5,6-dicarboxylate (76a) was reacted with potassium hydroxide using the above conditions, the same thiophen, 97, was obtained in 21% yield.

iii. Dimethyl 6-methyl-2,4-diphenyl-6H-*m*-dithiin (76c) was also subjected to the same treatment. In this case, however, the mixture obtained after several hours in contact with the potassium hydroxide still contained unchanged starting material. None of the components of the mixture could be isolated by chromatography due to poor resolution and streaking.

iv. A solution of dimethyl *trans*-3,4-dihydro-3,4-diphenyl-*o*-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) in dichloromethane (25 ml) was treated under the same phase-transfer conditions with potassium hydroxide then methyl iodide (excess). Work-up after 1 hour gave a foul smelling oil which crystallised

as colourless needles on treatment with methanol. The product was identified (nmr, mixed melting point) as dimethyl 2,3-diphenylthiophen-4,5-dicarboxylate (91; 0.074g, 21%); mp. 93° (lit.[133] 85°).

No evidence of ester hydrolysis was found in any of the above reactions.

B. Treatment with acids

a. Concentrated hydrochloric acid

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) was heated on a steam bath for 1 hour with concentrated hydrochloric acid (30 ml). The reaction mixture was diluted with water and extracted with dichloromethane. Evaporation of solvent under reduced pressure gave unchanged starting material (0.35g, 91%).

b. Concentrated sulphuric acid

The above procedure was adopted, using concentrated sulphuric instead of hydrochloric acid. On dilution with water, a pink precipitate appeared, which was shown to be starting material. Thin-layer chromatography indicated that some reaction had occurred forming a mixture, but in spite of this, unchanged m-dithiin 70a was recovered in 88% yield.

c. Formic acid

No reaction was observed when m-dithiin, 70a, was heated under reflux in formic acid; an 85% recovery of unchanged starting material was attained.

Similarly, no reaction was observed when dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69) was heated with the same acids.

m-Dithiin 70a was treated with the following reagents:

a. Concentrated ammonia

Concentrated ammonia (d 0.88; 5.0 ml) was added to a stirred solution of m-dithiin, 70a (0.39g, 1.0mmol), in THF (30 ml) at room temperature. A mixture began to form immediately, and after 20 minutes, all starting material had been consumed. The mixture was extremely complex and the odorous brown oil produced on work-up could not be crystallised.

b. Trimethylsilyl iodide

A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry (ethanol-free) chloroform (15 ml) was stirred at room temperature under nitrogen. Trimethylsilyl iodide (0.57 ml, 4.0mmol) was added dropwise, and after 10 hours, it was shown (thin-layer chromatography) that no reaction had taken place.

c. Potassium thiocyanate

Potassium thiocyanate (0.39g, 4.0mmol) was added to a solution of m-dithiin, 70a (0.39g, 1.0mmol), in dimethylformamide (15 ml). No reaction had taken place after 2 hours at room temperature, and so the solution was heated under reflux for 1 hour. Dilution with water followed by extraction with dichloromethane yielded a vile smelling fraction which was shown to contain many components.

d. Sodium thiophenoxide

Thiophenol (2.2g, 20mmol) was added slowly, with cooling, to a stirred solution of sodium ethoxide (1.36g, 20mmol) in ethanol (10 ml). A white solid precipitated, and the excess solvent was evaporated under reduced pressure. The product, sodium thiophenoxide (2.35g, 85%), was washed with ether and dried under vacuum in a desiccator.

A solution of m-dithiin, 70a (0.39g, 1.0mmol), in dimethylformamide (10 ml) was stirred at 35° and sodium thiophenoxide (0.53g, 4.0mmol) was added. All starting material had been consumed after 1½ hours, and a complex mixture had formed. The solution was diluted with water and extracted with dichloromethane to give, after evaporation of solvent, a brown oil which could not be crystallised. No bicarbonate soluble material was present.

21. Preparation of m- and o-Dithiin Anhydrides and Their Derivatives

Treatment of m-dithiin, 70a, with boron trifluoride etherate

i. A solution of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.39g, 1.0mmol) in dry toluene (20 ml) was treated with freshly distilled boron trifluoride etherate (40%; 1.2 ml) and then heated under reflux for 6 hours. It was found that the only reaction which had taken place was the thermal rearrangement to o-dithiin, 69.

ii. The experiment was repeated using toluene to which water (0.5 ml) had been added. It was found that after heating under reflux for 1½ hours, all starting material had been consumed, and a new, less polar component had formed. The reaction mixture was allowed to cool, was washed repeatedly with water then dried ($MgSO_4$). Evaporation of the solvent in vacuo afforded a yellow oil which crystallised as colourless prisms (mp. 155-156°) on treatment with ether. The product was identified by ir, nmr, and mass spectroscopic analysis as 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylic anhydride (103; 0.34g, 87%). (Found: C,63.3; H,3.5; S,18.9. $C_{18}H_{12}O_3S_2$ requires C.63.5; H,3.5; S,18.8%), $^M/_e$ 340.

δ,ppm($CDCl_3$):	7.4(s,C_6H_5)
	5.29,5.11(s,H-2,H-4)
νmax,cm^{-1}:	1843,1786 (CO.O.CO)

Treatment of o-dithiin, 69, with boron trifluoride etherate

Dimethyl trans-3,4-dihydro-3,4-diphenyl-o-dithiin-5,6-dicarboxylate (69; 0.39g, 1.0mmol) was dissolved with warming in toluene (20 ml) which contained water (0.5 ml). Boron trifluoride etherate (1.2 ml) was added, and the solution was heated under reflux for 2 hours. The solution was allowed to cool, was washed with water, then dried ($MgSO_4$). Evaporation of the solvent in vacuo gave a yellow oil which crystallised as colourless prisms on treatment with ether. The product was identified as 3,4-dihydro-3,4-diphenyl-o-dithiin-5,6,-dicarboxylic anhydride (179; 0.33g, 85%) and had mp. 125-126°. (Found: C,63.6; H,3.5; S,18.9. $C_{18}H_{12}O_3S_2$ requires C,63.5; H,3.5; S,18.8%), ^{M}/e 340.

δ ,ppm($CDCl_3$):	7.23 (m,C_6H_5)
	4.41,4.26(d,H-3,H-4, J=6.5Hz)
ν max, cm^{-1}:	1842, 1778 (CO.O.CO)

Treatment of m-dithiin monoester, 70b, with boron trifluoride etherate

Methyl 2,4-diphenyl-4H-m-dithiin-5-carboxylate (70b; 0.33g, 1.0mmol) was treated with boron trifluoride etherate (1.2 ml) in 'wet' toluene (20 ml) as described above. Heating under reflux for 3 hours produced no change in the starting material, but after 8 hours' reflux, the reaction mixture had become very dark in colour and thin-layer chromatography indicated the presence of a more polar component. In addition, there were two

components which showed fluorescence under uv light. The solution was allowed to cool, was washed with water, and extracted with aqueous sodium bicarbonate. The aqueous extracts, on acidification gave a small amount of brown oil which was insufficient for analysis.

Reaction of 2,3-dihydrothiophen, 169, with boron trifluoride etherate

Dimethyl cis-2,3-dihydro-2,3-diphenylthiophen-4,5-dicarboxylate (169; 0.35g, 1.0mmol) was treated with boron trifluoride etherate (1.2 ml) in 'wet' toluene (20 ml) as described above. Heating under reflux for 10 hours resulted in the formation of a more polar component, but most of the starting material remained unchanged. The consumption of starting material thereafter did not appear to increase, and so the reaction mixture was allowed to cool, was washed with water and extracted with aqueous sodium bicarbonate. The aqueous extracts were acidified and the solid produced was removed by filtration and recrystallised from aqueous methanol. The colourless needles thus produced were identified as 5-methoxycarbonyl-2,3-dihydro-2,3-diphenylthiophen-4-carboxylic acid (180; 0.04g, 12%) and had mp. 155-157°; $^{M}/e$ 340.

δ, ppm($CDCl_3$): 7.15(m, C_6H_5)
5.66, 4.84(d, H-2, H-3 J=9.5Hz)
4.08(s, CO_2CH_3)

νmax, cm^{-1}: 1740 (CO_2Me)
1678 (CO_2H)

In addition, 75% of unchanged starting material was recovered.

Treatment of the 6H-tautomeric m-dithiin, 76a, with boron trifluoride etherate

A solution of dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a; 0.39g, 1.0mmol) in 'wet' toluene (20 ml) was treated with boron trifluoride etherate in the way described above. It was shown by thin-layer chromatography that after 25 minutes' reflux, a 4- or 5-component mixture was present; work-up as in the previous experiment afforded 5-methoxycarbonyl-2,4-diphenyl-6H-m-dithiin-6-carboxylic acid (105; 0.08g, 21%) as colourless prisms with mp. 214-216°; M/e 372

δ, ppm($CDCl_3$):	9.72 (s, CO_2H)
	7.38 (s, C_6H_5)
	5.66, 5.04 (s, H-2, H-6)
	3.91 (s, CO_2CH_3)
ν max, cm^{-1}:	1725 (CO_2Me)
	1690 (CO_2H)

Reaction of m-dithiin half ester, 84*, with boron trifluoride etherate

6-Methoxycarbonyl -2,4-dipheny-6H-m-dithiin-5-carboxylic acid (84; 0.37g, 1.0mmol) was treated with boron trifluoride etherate in the presence of water as previously described. A mixture of several components

* prepared by the reaction of m-dithiin, 70a with n-butyllithium in the presence of DABCO, page 56 .

was shown to be present after refluxing for 30 minutes. The solution was allowed to cool, was washed repeatedly with water then dried. Evaporation of the solvent under reduced pressure afforded a brown oil which formed pale yellow prisms on treatment with ether. The product, 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylic anhydride (106, 0.04g, 13%) had mp. 136°; $^{M}/_{e}$ 340.

δ ,ppm ($CDCl_3$):	7.42,7.22 (s,C_6H_5)
	5.67,5.03 (s,H-2,H-6)
νmax, cm^{-1}:	1820,1762 (CO.O.CO)

The following esters were treated with boron trifluoride etherate under the normal conditions for anhydride formation.

i. Di-n-butylphthalate gave phthalic anhydride in 78% yield after refluxing in 'wet' toluene for 5 hours.

ii. Methyl benzoate afforded benzoic acid in 7% yield after heating under reflux for 16 hours.

iii. Dimethyl maleate gave no apparent reaction after 10 hours' reflux.

Reaction of m-dithiin anhydride, 103, with methanol

A stirred solution of 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylic anhydride (103; 0.34g, 1.0mmol) in hot methanol (25 ml) was treated with concentrated sulphuric acid (0.5 ml). The reaction mixture was heated under reflux for 3½ hours then allowed to cool. Colourless needles of dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a; 0.37g, 96%) separated and were identified by mixed melting point and nmr spectroscopy.

2,4-Diphenyl-4H-*m*-dithiin-5,6-dicarboxylic acid (96)

2,4-Diphenyl-4H-*m*-dithiin-5,6-dicarboxylic anhydride (103; 0.34g, 1.0mmol) was dissolved with warming in a 2 molar solution of sodium hydroxide (10ml). The solution was slowly acidified to pH 6 with concentrated hydrochloric acid and the solid which had formed was removed by filtration and dried under vacuum in a desiccator. Nmr spectroscopic analysis was impossible due to solubility problems, but the product diacid, 96 (0.33g, 91%), was identified by infrared spectroscopy and had mp. 198° (gas evolved on melting).

(During recrystallisation from aqueous methanol, the parent anhydride 103 was reformed; the same dehydration was observed during mass spectroscopic analysis.)

ν max, cm^{-1}: 2900-2400 (OH acid)
1690,1660 (CO_2H)

3,4-Dihydro-3,4-diphenyl-*o*-dithiin-5,6-dicarboxylic acid (178)

3,4-Dihydro-3,4-diphenyl-*o*-dithiin-5,6-dicarboxylic anhydride (179: 0.34g, 1.0mmol) was treated with sodium hydroxide as described in the previous experiment and then acidified. The title compound, 178, precipitated (0.3g, 84%); it was dried under reduced pressure in a desiccator, and had mp. 137-139° (gas evolved on melting).

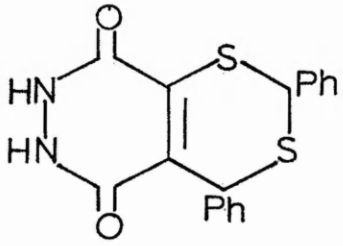
(Once again, no nmr spectrum was obtained due to insolubility, and during recrystallisation and mass spectroscopic analysis, the parent anhydride, 179, was reformed.)

ν max, cm^{-1}: 2900-2500 (OH acid)
1738,1686 (CO_2H)

2,4-Diphenyl-4H-m-dithiino -5,6,pyridazinedione (107)

A solution of 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylic anhydride (103; 0.34g, 1.0mmol) in THF (30 ml) was treated with hydrazine hydrate (0.08g, 1.5mmol). The reaction was complete after heating under reflux for 1 hour. On cooling, the product 107 separated as a white solid; this was removed by filtration, washed with water, then methanol, and dried in vacuo (0.08g, 23%); mp. 178-180°; M/e 354.

ν max, cm^{-1}: 3310,3288 (NH amido)
1662 (CONH)



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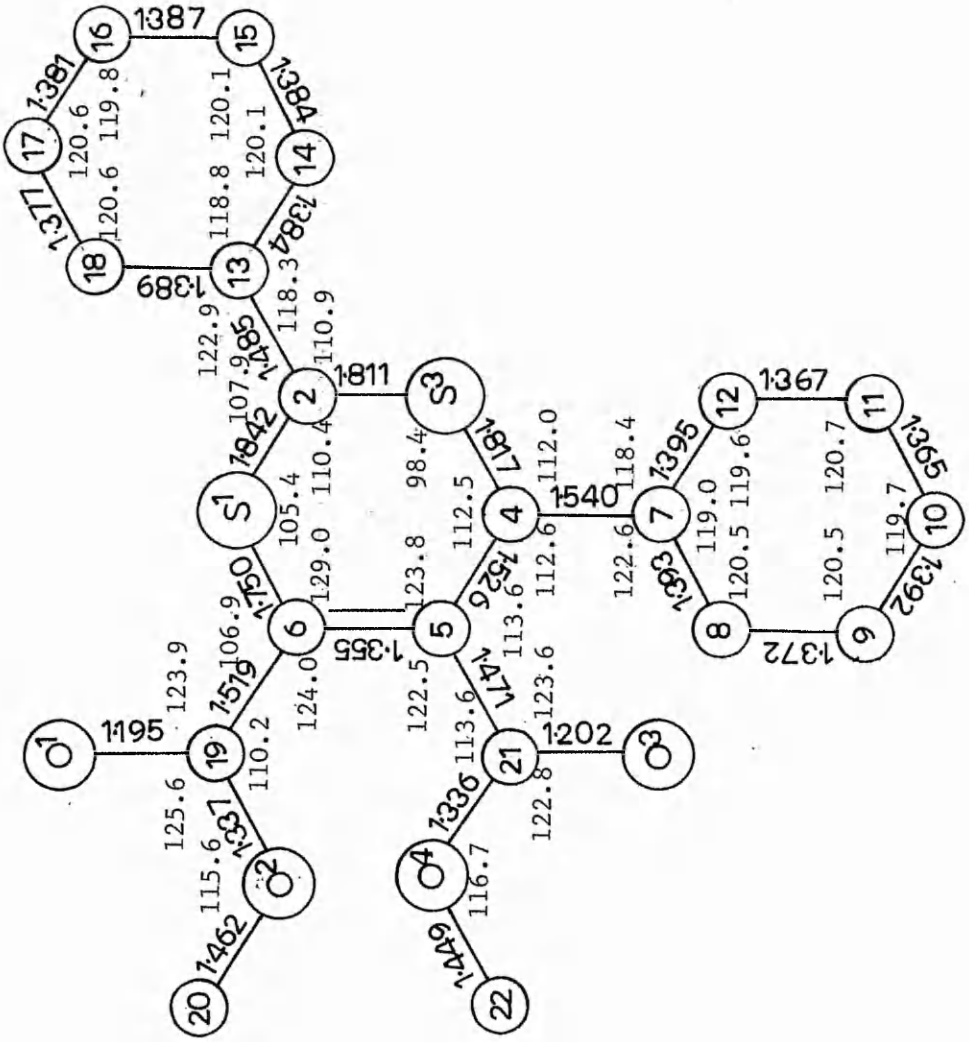
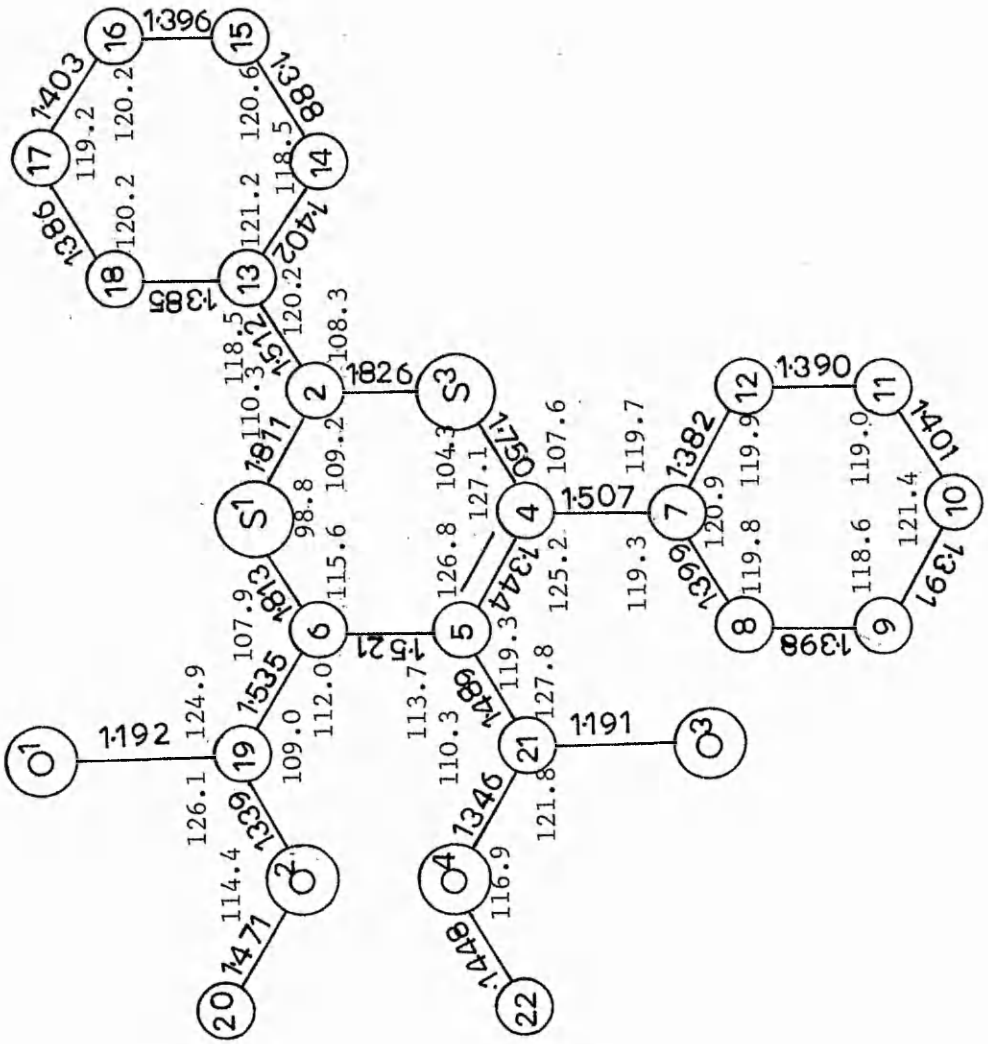
APPENDIX A.

X-ray crystallographic data

Dimethyl 2,4-diphenyl-4H-m-dithiin-5,6-dicarboxylate (70a)

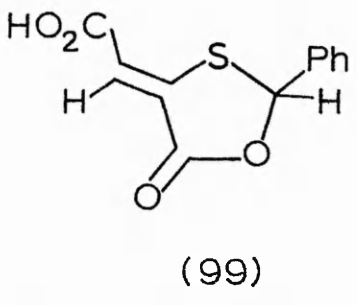


Dimethyl 2,4-diphenyl-6H-m-dithiin-5,6-dicarboxylate (76a)

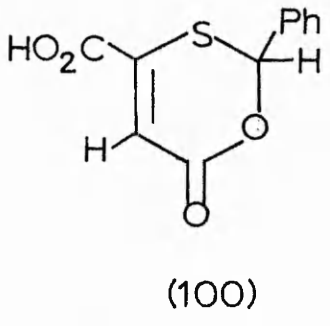


APPENDIX B.

The following two spectroscopic methods were used as means of identifying the product of the reaction between acetylene dicarboxylic acid and 2,4,6-triphenyl-1,3,5-trithiane (page 82). The possible structures (99 and 100) are shown below.



(99)



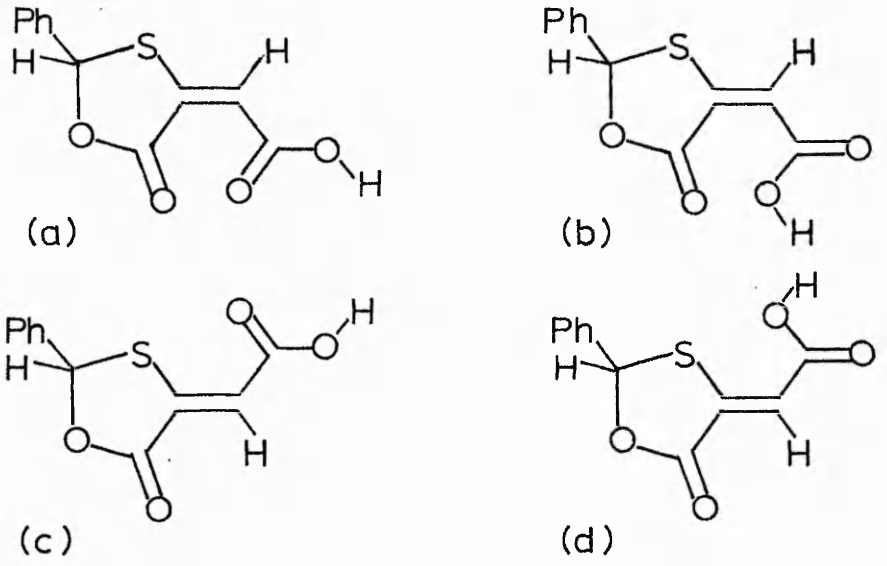
(100)

1. Infrared spectroscopy (for data, see Table 6)

Carboxylic acids dimerise in solution to an extent which depends on concentration, and so multiple frequencies are expected whose relative intensity will change on dilution. This fixes the acid carbonyl as being responsible for the set of bands of variable intensity at and above 1680 cm^{-1} (in solution). The remaining carbonyl stretching frequency at 1770 cm^{-1} must therefore be due to the lactone group; this frequency is about that expected for a 5-membered lactone[144]. The lactone - carbonyl frequency for the 6-membered structure (100) is calculated to be 1685 cm^{-1} [139], and on this basis the 5-membered lactone structure, 99, is strongly favoured.

The precise alignment of the carboxylic acid function relative to the ring carbonyl group in 99 is more difficult to assign. The four possibilities are as

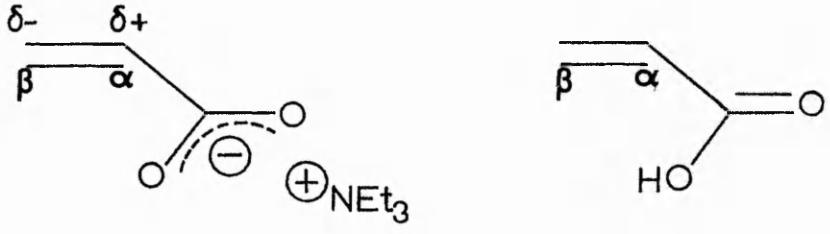
follows:



Since conjugation in the trans forms, a and b is maximised, one of these may seem the most likely arrangement. Structure a should be disfavoured because of strong electrostatic repulsion between adjacent carbonyl groups; structure b should exhibit strong intramolular hydrogen bonding because of the proximity of the lactone carbonyl and hydroxyl groups. The dilution experiments however, clearly show that the acid is inter- rather than intramolecularly hydrogen bonded (evidenced by the appearance, on dilution, of a new 'free acid' absorption at 1730 cm^{-1}). This leaves c and d to be considered; of these, d is unlikely, since the lone pair-lone pair repulsion will be more severe. Structure c is therefore the favoured conformation, and a similar structure has been found in analogous cases[64].

2. ^{13}Cnmr spectroscopy (for data, see Table 7)

When an acrylic acid is treated with a base such as triethylamine, the carboxylate anion which is formed induces a change in the polarisation of the olefin; the α carbon experiences an increased positive charge and the β carbon experiences an increased negative charge.



These changes are reflected in the ^{13}C spectrum by a downfield shift in the α carbon signal and an upfield shift in the β carbon signal relative to those in the free acid. Since the α and β carbon atoms in the cyclic lactone are distinguishable in the ^{13}C spectrum, (one carries a hydrogen atom, and the other does not), then their shifts on salt formation should indicate their position (and hence the ring size of the lactone). These shifts were measured, together with those of representative acrylic acids (Table 7). The olefinic carbon which carries the proton experienced a downfield shift, and was thus identified as the α carbon. Conversely, the fully substituted olefinic carbon moved upfield and was thus assigned as the β carbon. The conclusion is therefore that the 5-membered lactone structure, 99, is present.

Since both ir and ^{13}Cnmr analyses agree, there can be little doubt that this assignment is correct.

TABLE 6

ν max, cm^{-1}

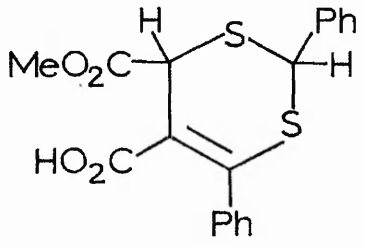
KBr.	nujol	CH_2Cl_2(conc.)	CH_2Cl_2(dil)	Assignment
3200-2300(m)	3200-2300(m)	3300-2500(w)		OH(acid)
1760(vs)	1760(vs)	1770(vs)	1770(vs)	C=O(lactone)
1673(s)	1673(s)	1705(w) 1678(m)	1730(w) 1708(mw) 1678(mw)	C=O(acid)
1600(m)	1600(m)	1603(m)	1603(m)	C=C

TABLE 7

^{13}C Data acrylic acid	shift relative to free acid on salt formation*(ppm)	
	α carbon	β carbon
$MeCH{=}CH.CO_2H$	+2.7	-6.8
$H_2C{=}CMe.CO_2H$	+3.3	-4.7
$PhCH{=}CH.CO_2H$	+4.7	-4.6
thiophen-2-carboxylic acid	+9.4	-4.7
thiophen-3-carboxylic acid	+6.9	-4.2(or-8.3)
99	+8.7	-10.4
84	+6.4	-4.7

* a positive sign indicates deshielding and a negative sign denotes shielding

The corresponding shifts for the α and β carbon atoms in compound 84 (Table 7) indicated that it is an acrylic acid.



(84)