CYCLOADDITION REACTIONS OF THIOXOACETATE ESTERS WITH UNSYMMETRICAL DIENES

A thesis presented in part fulfilment
of the requirements for the degree of
M.Sc.

by

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November 1987

Acknowledgements

I would like to thank my supervisor, Professor G.W. Kirby for all his help and guidance during the course of this research.

I also wish to thank my laboratory colleagues and the technical staff of the Chemistry Department for their assistance.

I am grateful to Dr. D.S. Rycroft for the 200 MHz ^{1}H n.m.r. spectra.

Finally, I would like to thank the Algerian Government for financial support and also my parents for their forbearance during my research.

CONTENTS

SUMMARY

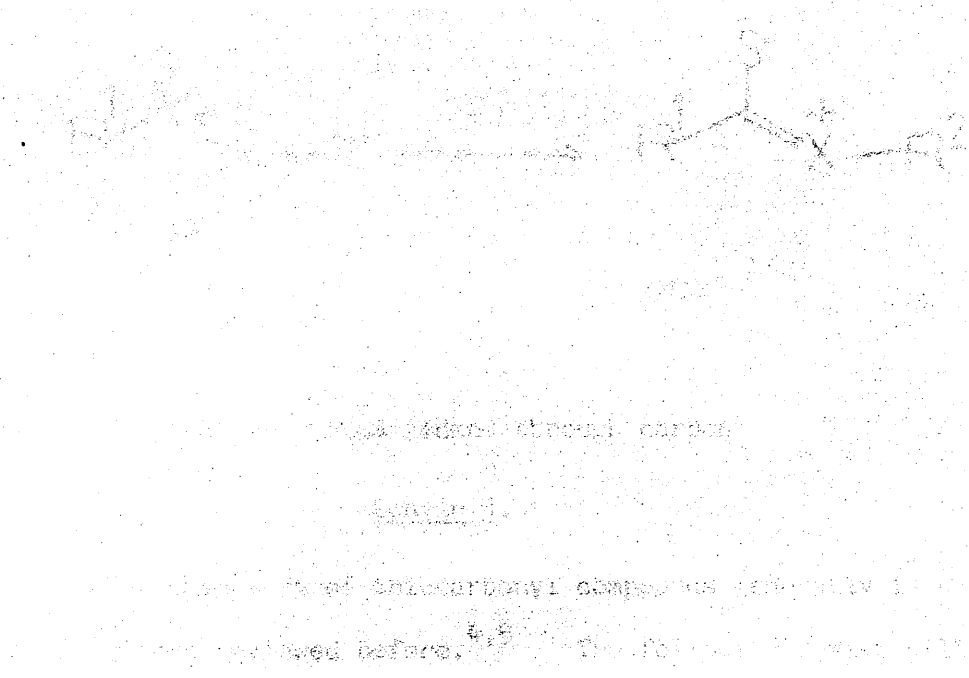
The Diels-Alder reaction of transient thioxoacetate esters, $RO_2C.CHS$, generated under mild, basic conditions from the Bunte salts, $RO_2C.CH_2SSO_3Na$, has been studied with a variety of unsymmetrical, conjugated dienes. Specifically, ethyl thioxoacetate was generated from the Bunte salt, $EtO_2C.CH_2SSO_3Na$, and trapped with 1-methoxy-1,3-cyclohexadiene, ethyl 3,5-hexadienoate, and the dienamine derived from Pummerer's ketone. Methyl 2,4-hexadienoate did not act as an effective trapping agent under these conditions. The regiochemistry, stereochemistry, and relative yields of the cycloadducts from each unsymmetrical diene are discussed.

The retro-Diels-Alder reaction has also provided a good method for the generation of thioxoacetate esters. Ethyl thioxoacetate was generated by thermal cleavage of the corresponding anthracene cycloadduct, and was trapped in situ with 1-methoxy-1,3-cyclohexadiene. Similarly, the cycloadduct of methyl 2,4-hexadienoate and methyl thioxoacetate was obtained in good yield using the corresponding anthracene adduct as a source of the thioaldehyde.

An intramolecular Diels-Alder reaction has been carried out successfully. The anthracene adduct of 3,5-hexadien-1-yl thioxoacetate was prepared by esterification of the corresponding acid. This cycloadduct dissociated in toluene at 111°C to liberate the unsaturated thioxoacetate ester, which cyclised to form the expected bicyclic lactone.

Competition reactions have been carried out to compare the reactivity of pairs of dienes. Treatment of a mixture of 1-methoxy-1,3-cyclohexadiene and 1,3-cyclohexadiene (1 mol equiv. of each) with the appropriate Bunte salt (1 mol equiv), and triethylamine, gave only the cycloadducts of ethyl thioxoacetate and the methoxydiene.

No significant amounts of the cycloadducts of cyclohexadiene were formed even when 2 mol equivalents of this diene were used. Again, 1-methoxy-1,3-cyclohexadiene, thebaine and the Bunte salt (1 mol equiv. of each) gave the corresponding cycloadducts of each diene in approximately equal amounts. Finally, treatment of 1,3-cyclohexadiene and methyl 2,4-hexadienoate with the Bunte salt in equimolar amounts gave only the cycloadducts of cyclohexadiene, thus confirming the low reactivity of the methyl 2,4-hexadienoate.

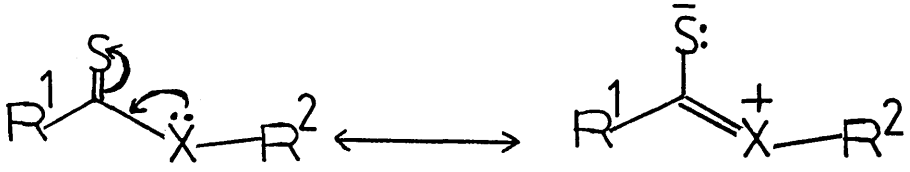


CHAPTER ONE

INTRODUCTION

1.1 Thioketones and Thioaldehydes.

Thioketones and thioaldehydes are compounds of the general structure, RR'C=S, where R and R' are either hydrogen or groups bonded through carbon. They are the least stable classes of thiocarbonyl compounds. The low stability and high polarizability of these compounds is believed to be due to the poor overlap between the carbon 2p and sulphur 3p orbitals.[1] The most stable thiocarbonyl compounds tend to be those in which the carbon of the thiocarbonyl group is directly bonded to an electron-donating group, as in thioamides[2] (1), thionoesters[1] (2), and dithioesters[3] (3). Stabilisation is brought about by the resonance of lone pair electrons between the electron-donating group and sulphur. This effect is shown in scheme 1.



(1) X = NR^3

(2) X = O

(3) X = S

R^1 and R^2 = H, or groups linked through carbon.

Scheme 1.

The chemistry of thiocarbonyl compounds generally is extensive and has been reviewed before.[4,5] The following review will concentrate mainly on thioaldehydes, the most reactive and labile class of thiocarbonyl compounds.

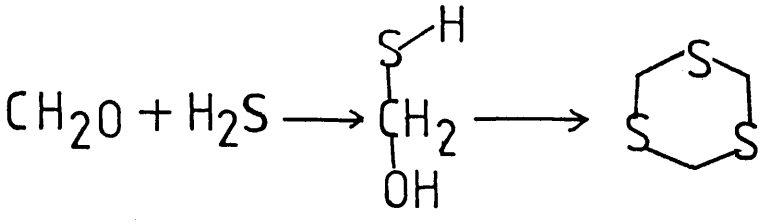
1.2 Synthesis of Thioaldehydes.

Early attempts to prepare thioaldehydes used the direct sulphurisation of the corresponding oxo-compounds with phosphorus pentasulphide or hydrogen sulphide, but these methods usually led to the isolation of polymeric materials. In 1868, Hofmann attempted the preparation of thioformaldehyde[6] (CH_2S) by treating formaldehyde (CH_2O) with a mixture of hydrogen sulphide and hydrochloric acid. He obtained a white solid compound (m.p. 218°C) for which he suggested the empirical formula $(CH_2S)_n$ (Scheme 2), but later this was identified as trithiane[7] $(CH_2S)_3$. One of the earliest proposals to account

$$CH_2O + H_2S \underset{\longleftarrow}{\overset{HCl}{\longrightarrow}} (CH_2S)_n + H_2O$$

Scheme 2.

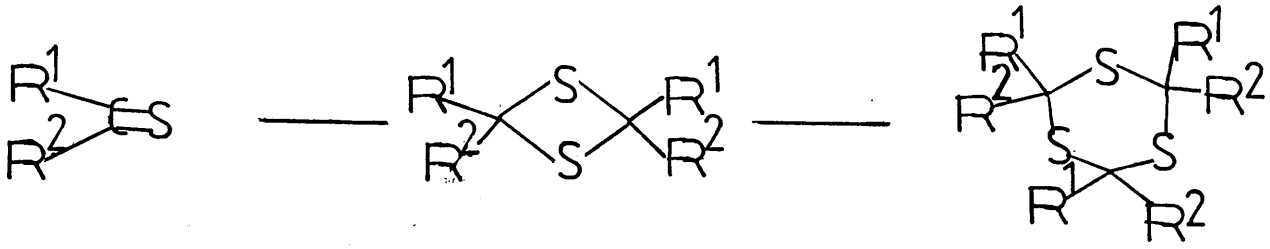
for the observed results was given by Baumann in 1890.[8] It was suggested that formation of the intermediate (5) can give rise to the trimer (4) as found by Hofmann (Scheme 3).



(5) (4)

Scheme 3.

Simple thioaldehydes have never been isolated in their monomeric forms, and were obtained as dimers (6) or trimers (7) when attempts to prepare them were made by Hofmann's method (Scheme 4). The same was true for simple thioketones.



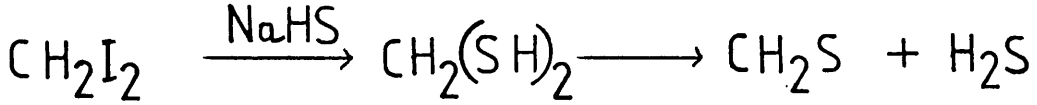
(6) (7)

R^1 = H, CH_3

R^2 = H, CH_3

Scheme 4.

Husemunn in 1863 attempted the preparation of thioformaldehyde[9] from methylene iodide and sodium hydrogen sulphide. On sublimation of the crude product, he obtained a white powder (m.p. 150°C). This he assumed to be di(methylene-sulphur) $(CH_2S)_2$ (8) (Scheme 5).

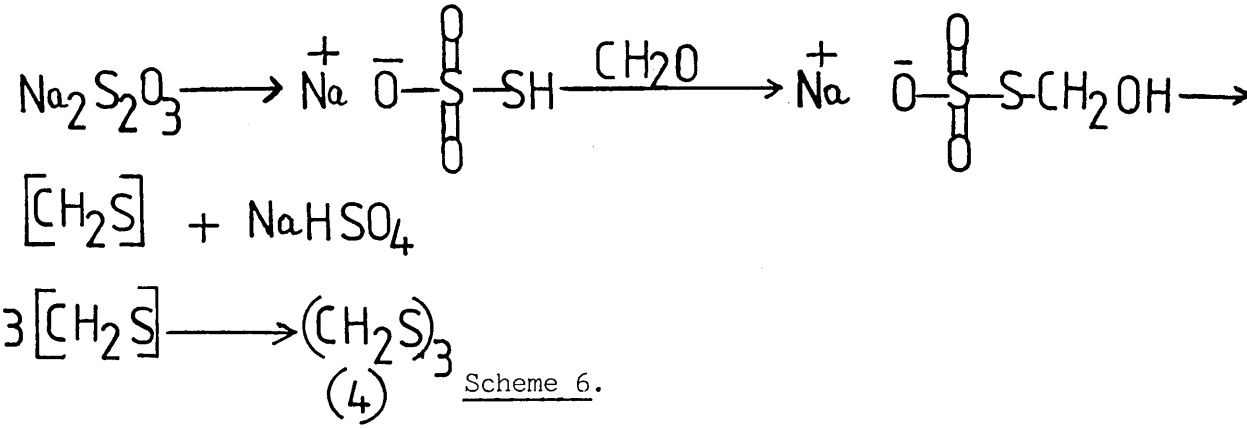


$(CH_2S)_2$

(8)

Scheme 5.

Vanino was able to isolate trithioformaldehyde[10,11] (4) by treating formaldehyde with a mixture of sodium thiosulphate and hydrochloric acid. The proposed mechanism for its formation is shown in Scheme 6.



(4)

Scheme 6.

Aromatic thioaldehydes (9) have been prepared in polymeric form using benzal halides (8) and metal sulphides (Scheme 7). In 1849 Cahours[12] treated benzal

$$\underset{(8)}{ArCHX_2} + Na_2S \longrightarrow \underset{(9)}{[ArCHS]} + 2NaX$$

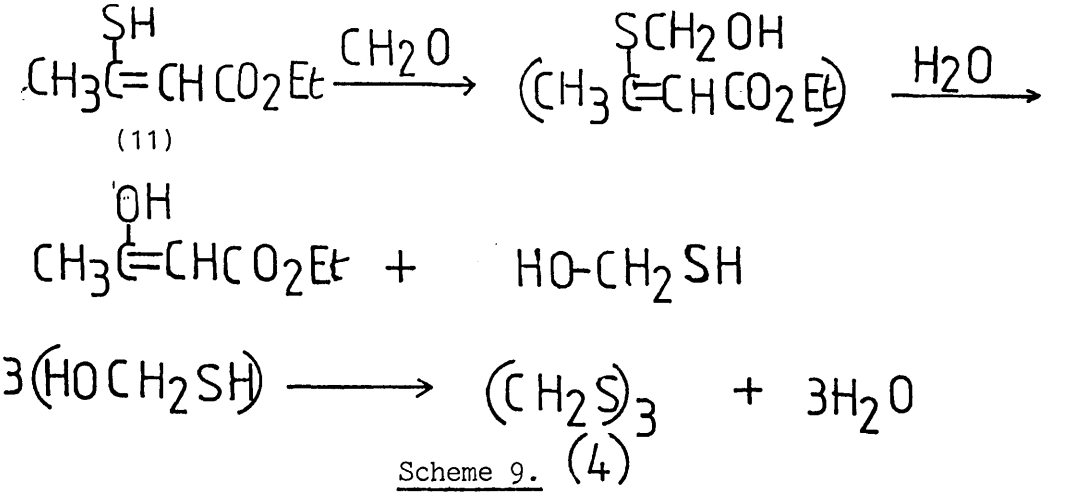
Scheme 7.

chloride with potassium hydrogen sulphide, and obtained a crystalline compound (m.p. 64°C) to which he assigned the formula $C_{14}H_6S_2$. Fleisher[13] performed the same reaction in boiling alcohol but obtained a higher melting compound (m.p. 68-70°C) which analysed correctly for thiobenzaldehyde. Klinger[14], later repeated the reaction using an excess of potassium hydrogen sulphide, and obtained dibenzyl disulphide (10) and dithiobenzoic acid (Scheme 8).

$$3C_6H_5CHCl_2 + 7KSH \longrightarrow \underset{(10)}{(C_6H_5CH_2S)_2} + C_6H_5CS_2K + 3H_2S + 6KCl$$

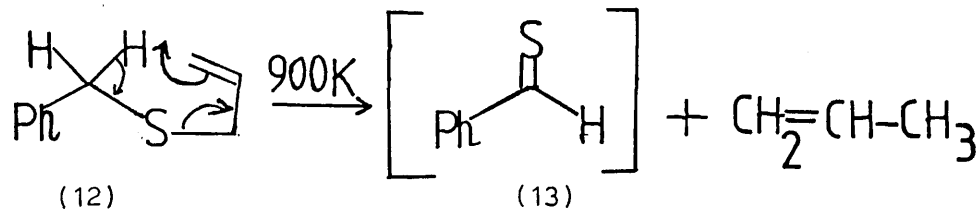
Scheme 8.

Another method for the formation of thioformaldehyde was investigated by Mitra[15]. He found that treating a saturated solution of ethyl thioacetoacetate (11) with dry hydrogen chloride at 0°C followed by addition of a 40% solution of formaldehyde with heating gave, not the desired thioaldehyde, but a trimer (4). The mechanism is shown in Scheme 9.



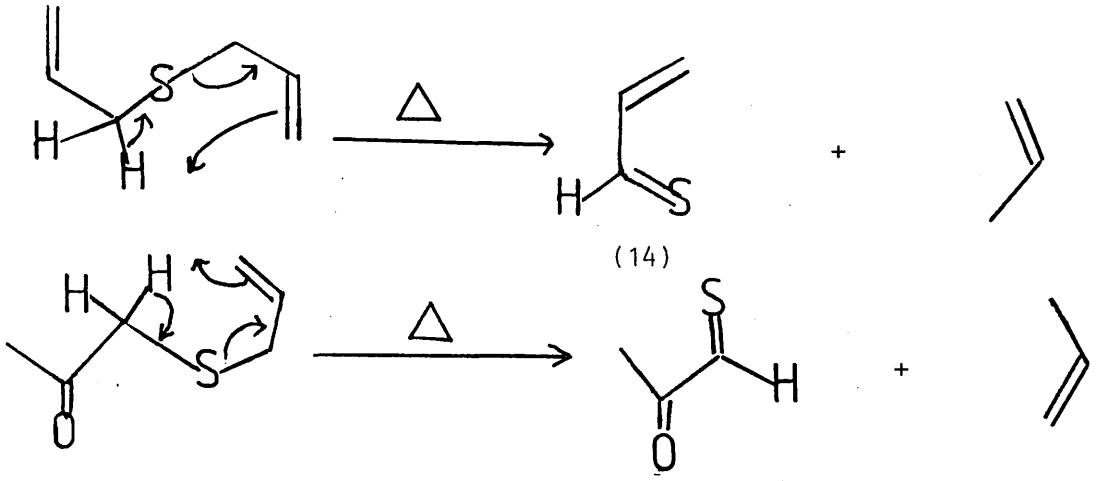
Scheme 9.

A suitable method for the preparation of thiobenzaldehyde (13) was achieved by de Mayo et al[16]. Flash vacuum thermolysis of allyl benzyl sulphide (12) afforded thiobenzaldehyde (13), which was condensed on a sodium chloride plate cooled with liquid nitrogen. This thioaldehyde was characterised by i.r. and u.v.-visible spectroscopy (Scheme 10).



Scheme 10.

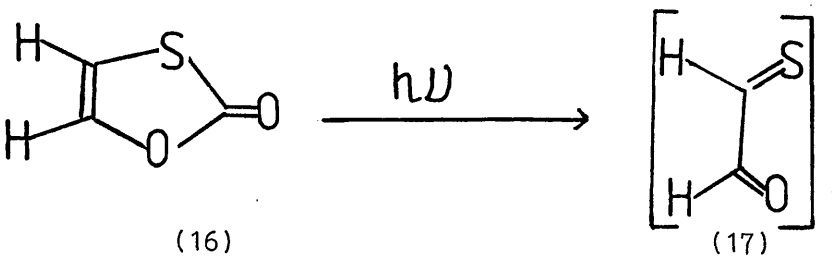
However, recent studies have shown that monomeric thioaldehydes may be trapped and identified spectroscopically at low temperatures. Thus, thioacrolein (14) and the thioacetaldehyde (15) were formed and isolated by using flash thermolysis techniques[17]. Their structures were elucidated from the electronic spectra at low temperatures (Scheme 11). Torres et al[18] isolated thioglycxal (17) by photolysis of vinylene thiocarbonate (16) in an argon matrix.



(14) (15)

Scheme 11.

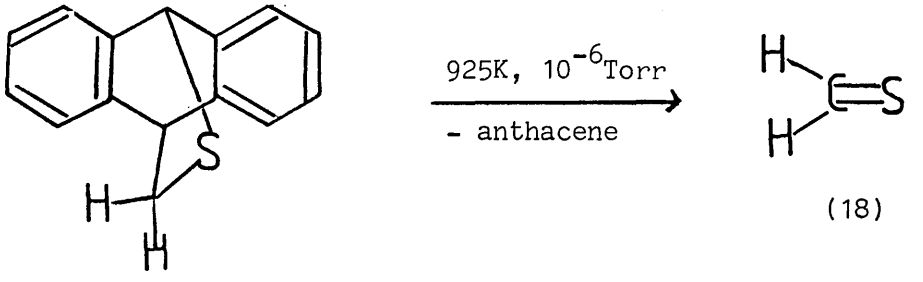
This thioaldehyde was stable enough at low temperature to be identified by u.v. and i.r. spectroscopy (Scheme 12).



(16) (17)

Scheme 12.

Recently Vallee and Ripoll reported[19] a convenient source of methanthial (18). Thus, flash vacuum pyrolysis of the anthracene adduct (19) afforded the thioaldehyde (18), which was identified in its monomeric form by the gas phase photoelectron analysis (Scheme 13).

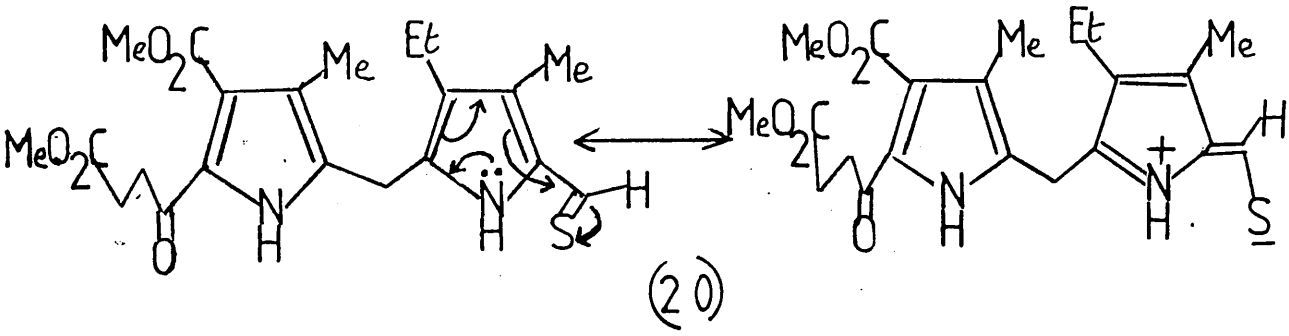


(19) (18)

Scheme 13.

The first stable thioaldehyde (20) of any kind to be reported was obtained by Woodward et al[20], in 1960, and was used as an important precursor in the total synthesis of chlorophyll a. The stability of (20) is thought to be due to the resonance caused

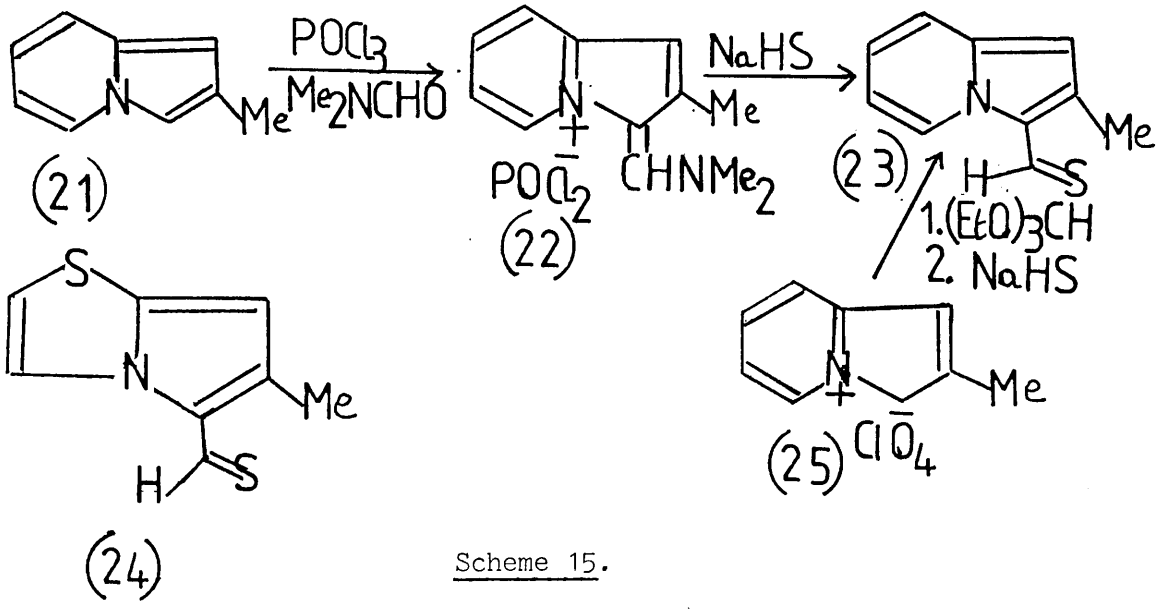
by conjugation of the thioformyl group with the electron-rich pyrrole. This effect is shown in Scheme 14. Similarly



(20)

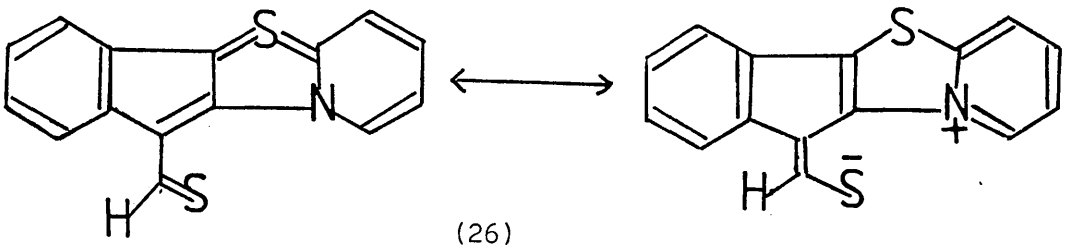
Scheme 14.

stabilised thioaldehydes (23) and (24) were reported by McKenzie and Reid[21]. They found that addition of phosphoryl chloride to a solution of 2-methylindolizine (21) in dimethylformamide at -60°C gave the Vilsmeier salt (22) which, when treated with aqueous sodium hydrogen sulphide (2M), gave 2-methyl-3-thioformylindolizine (24) as orange-red needles (m.p. 88-89°C). In similar fashion, they obtained 6-methyl-5-thioformylpyrrolo[2,1-b]thiazole (24). The compound (23) was also prepared by treating 2-methyl-3H-indolizinium perchlorate (25) with triethyl orthoformate and aqueous sodium hydrogen sulphide solution, as shown in Scheme 15. Reid et al[22,23,24] also extended



Scheme 15.

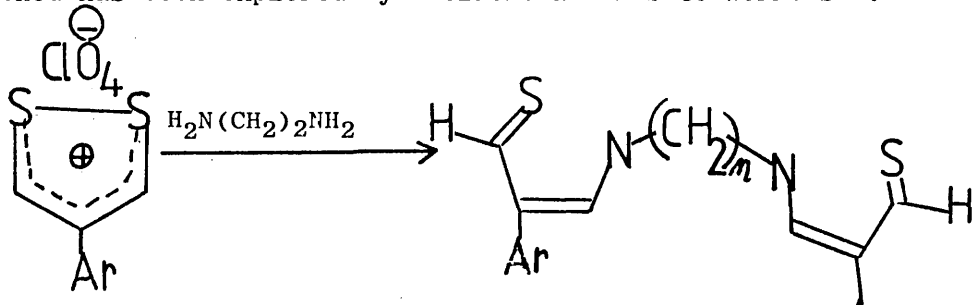
their method to the synthesis of other novel heterocyclic thioaldehydes (26). Here, the thioformyl group is conjugated to an extensive conjugated system which has an endocyclic tetravalent sulphur atom (scheme 16).



(26)

Scheme 16.

Holm and his colleagues[25] were able to prepare stable thioaldehydes (27) and (28) by treating 4-aryl-1,2-dithiolylium perchlorates (29) with primary and secondary amines (Scheme 17). These thioaldehydes, like those prepared by Woodward and by Reid et al, are presumably stabilised by electron donation from nitrogen. That is, they are effectively vinylogous thioformamides. Recently this method has been explored by Adelaere and his co-workers[26].



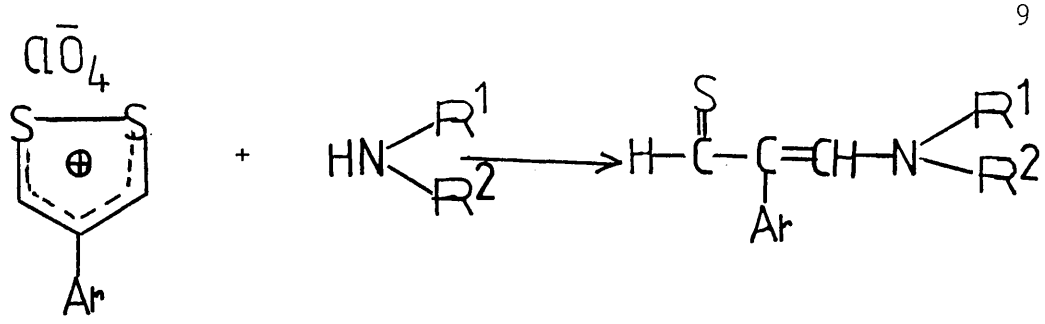
(29)

(27) n = 1

(28) n = 2

Scheme 17.

Thus, treatment of the perchlorates (29); Ar = C_6H_5, p-$CH_3C_6H_4$ with different amines gave the thioaldehydes (30) (Scheme 18).

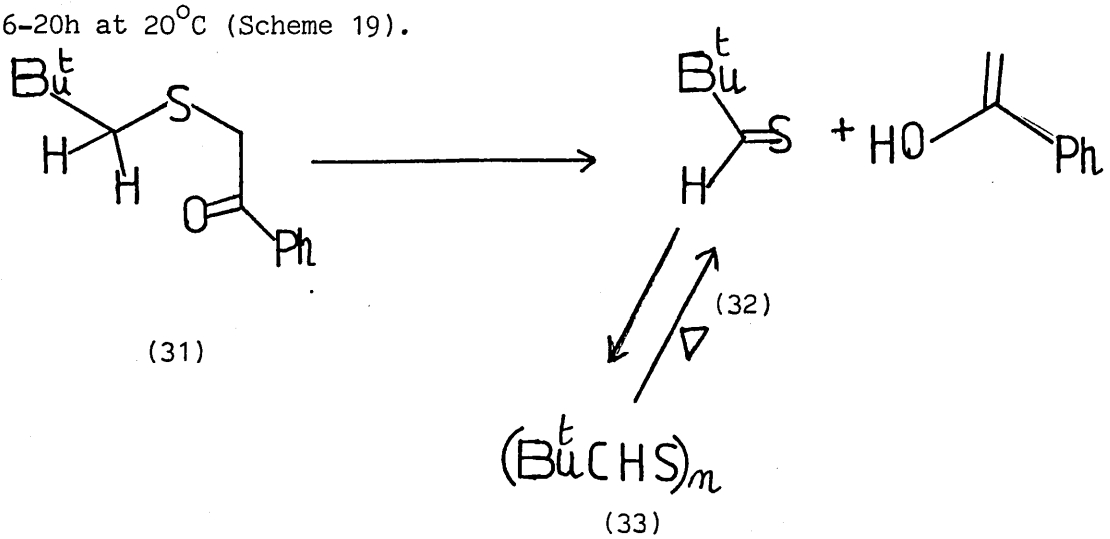


(29) (30)

a; R^2 = H
b; R^1, R^2 = H

Scheme 18.

It has recently been shown that thioaldehydes may be stabilised sterically and can then be isolated as their monomers. The first aliphatic thioaldehyde (32) observed under ordinary laboratory conditions was characterized by Vedejs et al[27] . The stability of this compound was thought to be due to the steric hinderance of the thiocarbonyl group. Photolysis of phenacyl sulphide (31) gave a polymer (33) which, when heated, gave the monomeric form of thiopivaldehyde(2,2-dimethylpropanethial) (32) in reasonable yield. This thioaldehyde survived in its monomeric form in solution for 16-20h at 20°C (Scheme 19).

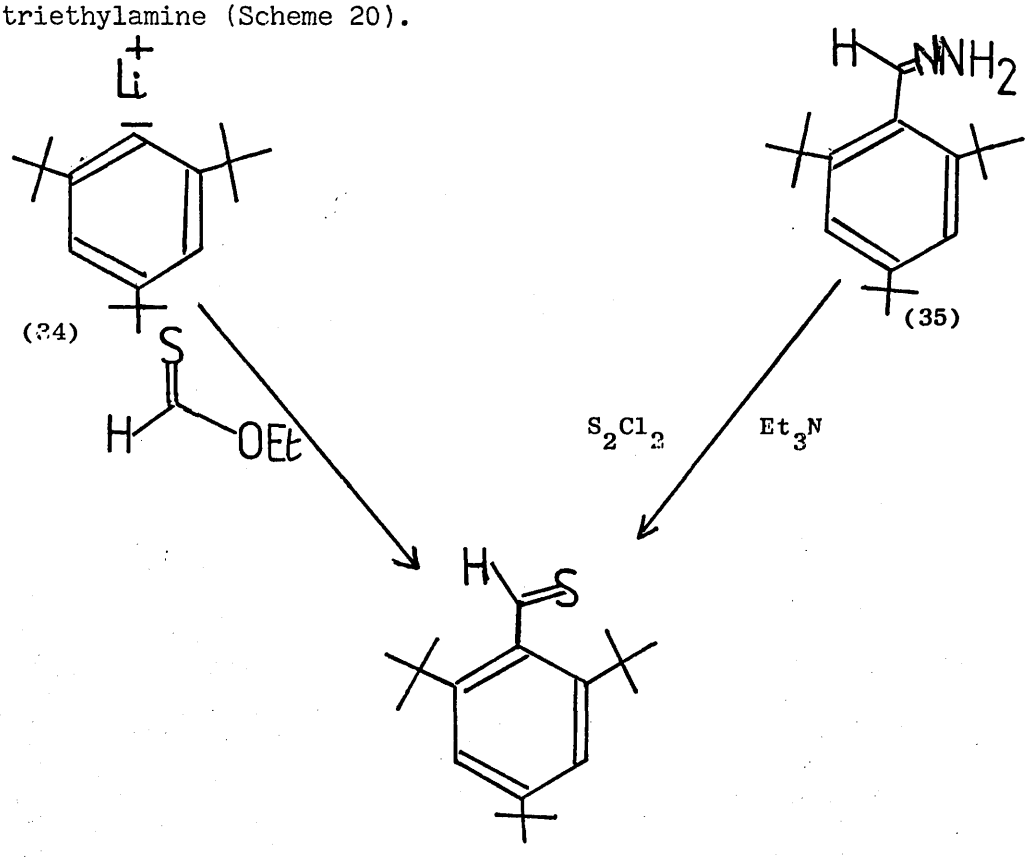


(31) (32) (33)

Scheme 19.

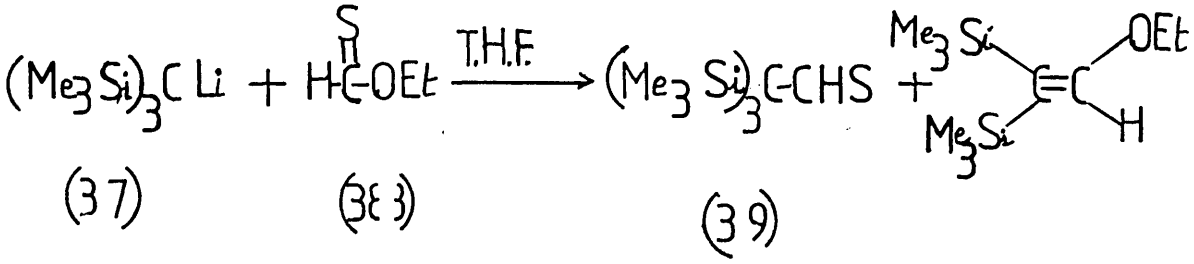
Two interesting methods have been reported for the preparation

of the thioaldehyde (36). Okajaki and co-workers[28] treated 2,4,6-tri-t-butylphenyl-lithium (34) with O-ethyl thioformate, whereas in the other method, they employed an oxidative sulphurisation of the hydrazone (35) with disulphur dichloride in the presence of triethylamine (Scheme 20).



Scheme 20.

The first isolable aliphatic thioaldehyde stabilised by steric hinderance rather than electronic effects has been reported very recently[29]. Thus, treatment of tris(trimethylsilyl) methyl-lithium (37) with O-ethyl thioformate (38) in tetrahydrofuran for 10 min at -78°C and for 1.5h at room temperature gave the thioaldehyde (39) in 16% yield (Scheme 21). This thioaldehyde was recrystallised at -78°C and gave pink - red crystals, m.p. 129 - 131°C. The thioaldehyde (39)



Scheme 21.

can survive for a long time in a refrigerator and at least for a week at room temperature.

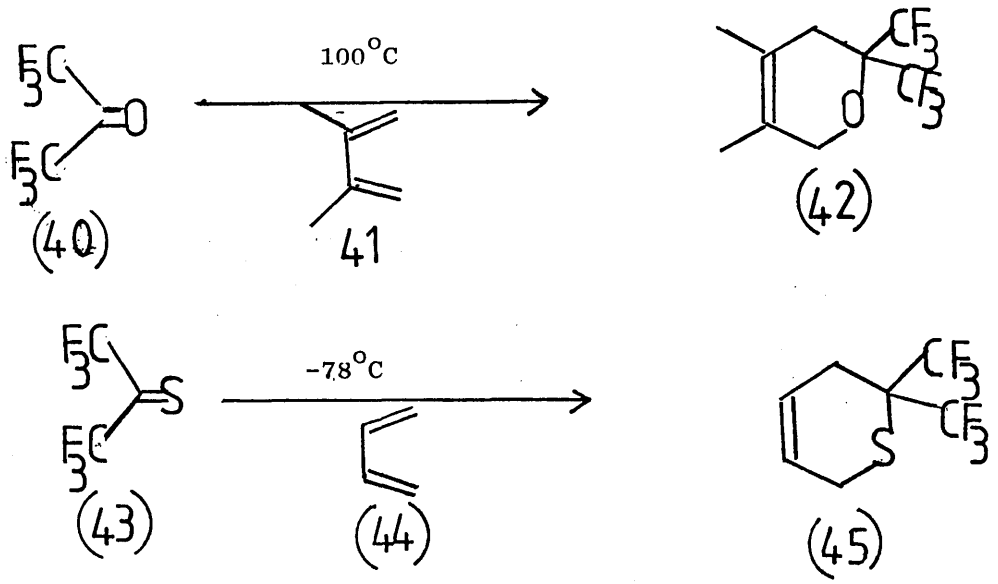
Recent developments in methods for the synthesis of simple, labile thioaldehydes have been stimulated by the potential use of these compounds as heterodienophiles in synthesis. These developments will be described after the Diels-Alder reactions of other classes of thiocarbonyl compounds have been briefly reviewed.

1.3 Thiocarbonyl Compounds as Dienophiles in 1,4-Cycloaddition. (Diels-Alder Reactions).

The first review on the cycloaddition reactions of thiocarbonyl compounds to appear in the literature was by Hamer and Turner[30] in 1967. At that time, there were very limited investigations in this particular field. However, although few thiocarbonyl compounds had been employed in 1,4-cycloaddition reaction, they showed considerable potential when only one new carbon-carbon bond was required in the products.

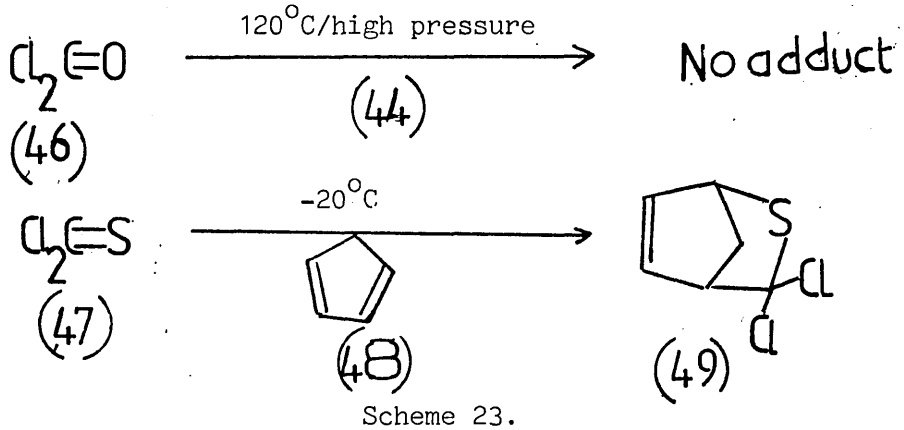
The reactivity of these dienophiles was found to be much higher than that of the corresponding oxo-compounds. For example, the reaction of hexafluoroacetone[31] (40) with 2,3-dimethyl-1,3-butadiene (41) at temperatures over 100°C gave the adduct (42), whereas hexafluoro-thioacetone[32] (43) reacted quantitatively with 1,3-butadiene (44) at -78°C to give the adduct (45) (Scheme 22). Similarly, phosgene[30] (46)

gave no cycloadduct with 1,3-butadiene (44) even at 120°C under



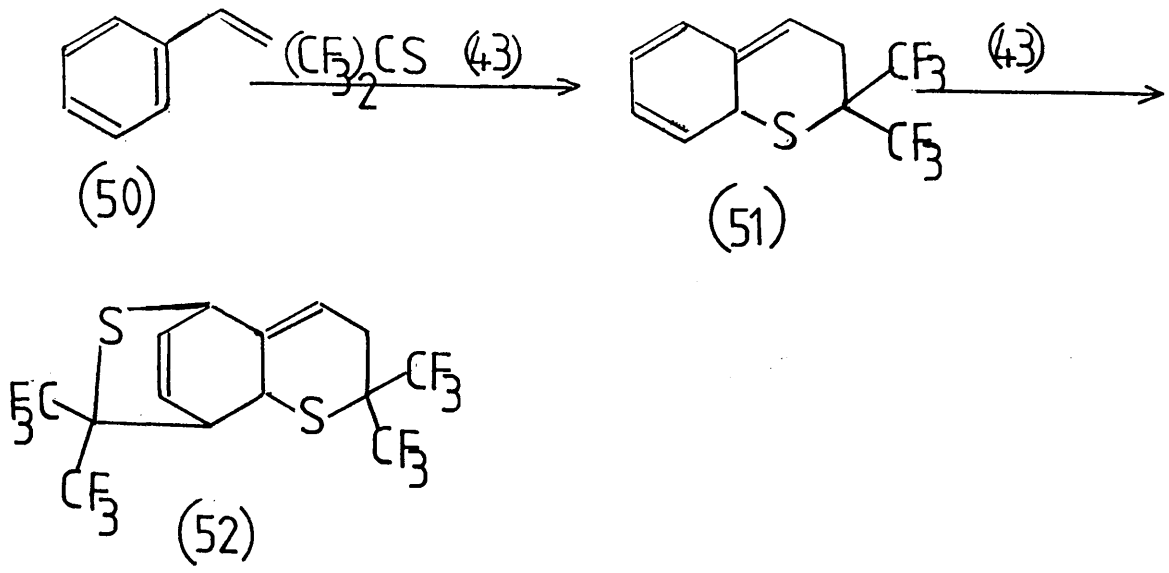
Scheme 22.

higher pressure, but thiophosgene[32] (47) reacted with cyclopentadiene (48) at -20°C to give the adduct (49) (Scheme 23).



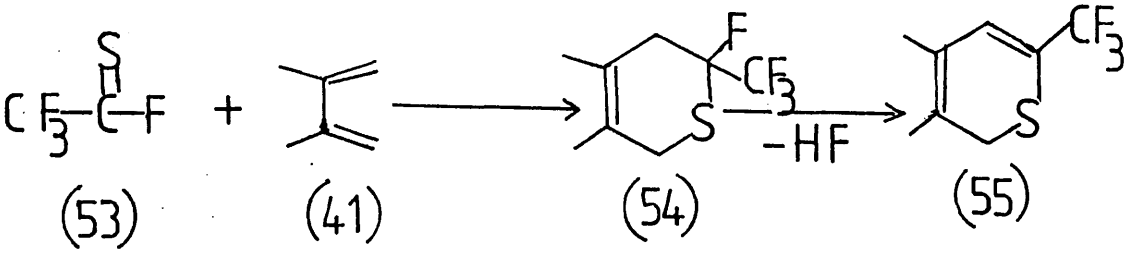
Scheme 23.

The 1,4-cycloaddition reactions of a wide variety of fluorothiocarbonyl compounds were studied by Middleton et al[33]. They found that hexafluorothioacetone (43) reacted easily with furan and anthracene. With styrene (50) the adduct (51) was initially formed, and further reacted with another molecule of (43) to give the adduct (52) (Scheme 24).



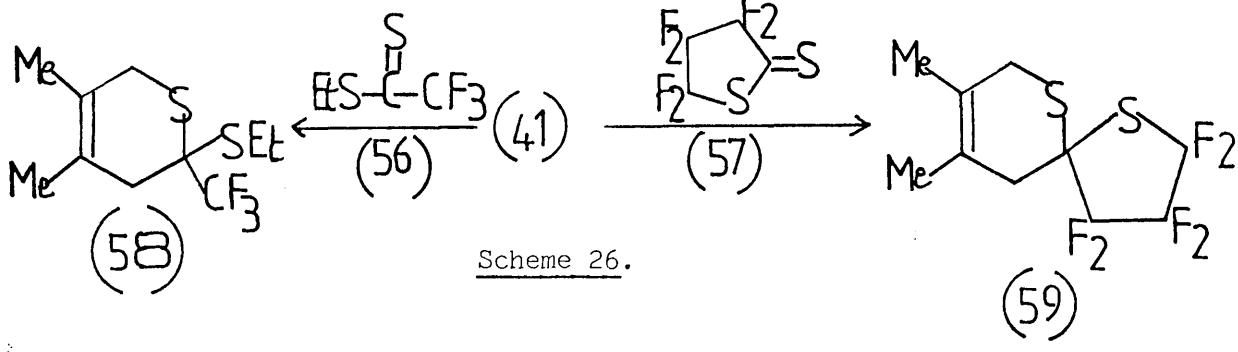
Scheme 24.

It was found that thioacyl fluorides were also reactive dienophiles. Treatment of trifluorothioacetyl fluoride (53) with butadiene (44) or dimethylbutadiene (41) led to the corresponding dihydrothiopyrans (54). These adducts were found to be unstable. They lost hydrogen fluoride easily to give thiopyrans (55) (scheme 25).



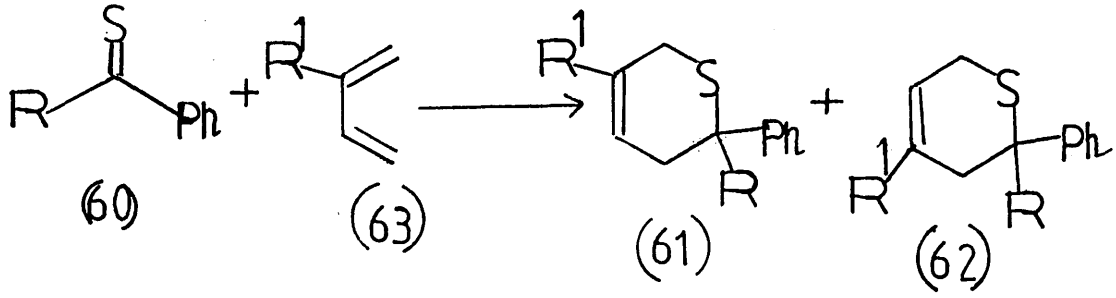
Scheme 25.

In addition to the previous dienophiles, dithioesters[33] having electron-withdrawing groups were found to be good dienophiles in Diels-Alder cycloaddition. Ethyl trifluorodithioacetate (56) and perfluorodithiobutyrolactone (57) reacted with dimethylbutadiene (41) at 0°C to give the adducts (58) and (59) respectively (Scheme 26).



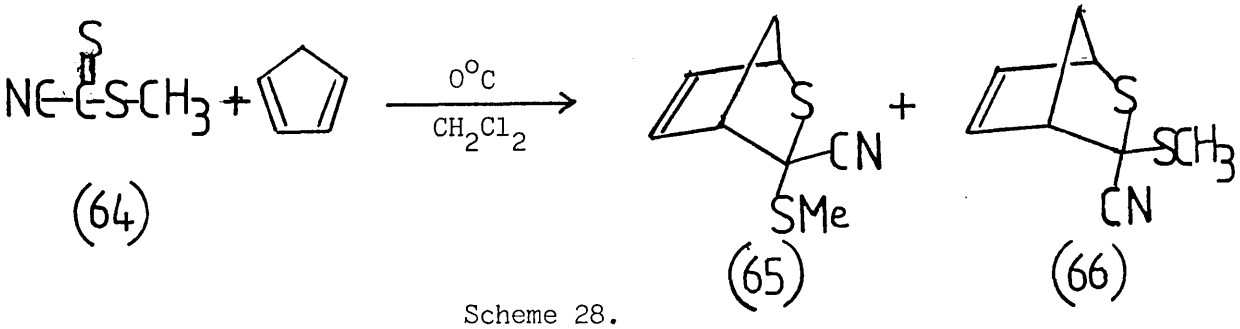
Scheme 26.

Yamada et al studied the photochemical reaction of thiobenzophenone with conjugated dienes[34]. They found that thiobenzophenone reacted with isoprene or cyclopentadiene with ultraviolet irradiation at -78°C and only when the reaction mixture was exposed to the light. Ohno and his colleagues[35] found that the thioketones (60) gave Diels-Alder adducts (61) and (62) with 2-substituted and unsubstituted 1,3-butadiene (63). The product ratios were determined from integration of ^1H n.m.r. spectra (Scheme 27).



Scheme 27.

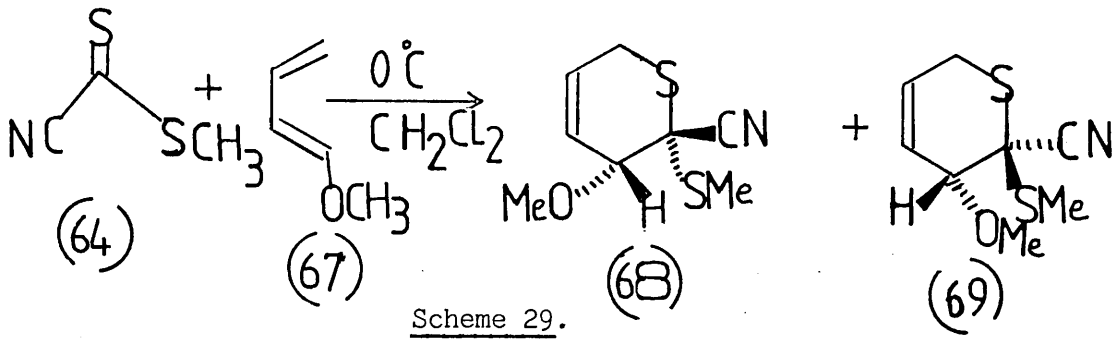
Vyas and Hay, used methyl cyanodithioformate[36,37] (64) as a reactive dienophile in Diels-Alder reactions. The advantage of this compound was the introduction of an extra functional group (cyano) into the products. Treatment of (64) with cyclopentadiene at room temperature resulted in an excellent yield of the cycloadducts (65) and (66) (Scheme 28). The product ratio was 6:4, exo-cyano: endo-cyano. Similarly, the dithioester (64) reacted with



Scheme 28.

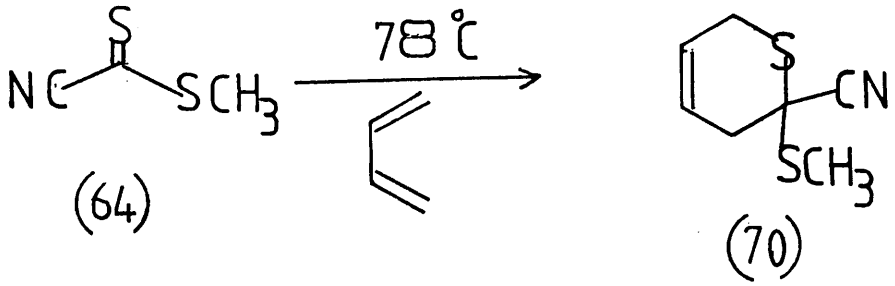
trans-1-methoxy-1,3-butadiene (67) regiospecifically and gave a good yield of the Diels-Alder adducts (68) and (69) (Scheme 29).

Similarly, treatment of the dienophile (64) with 1,3-butadiene at



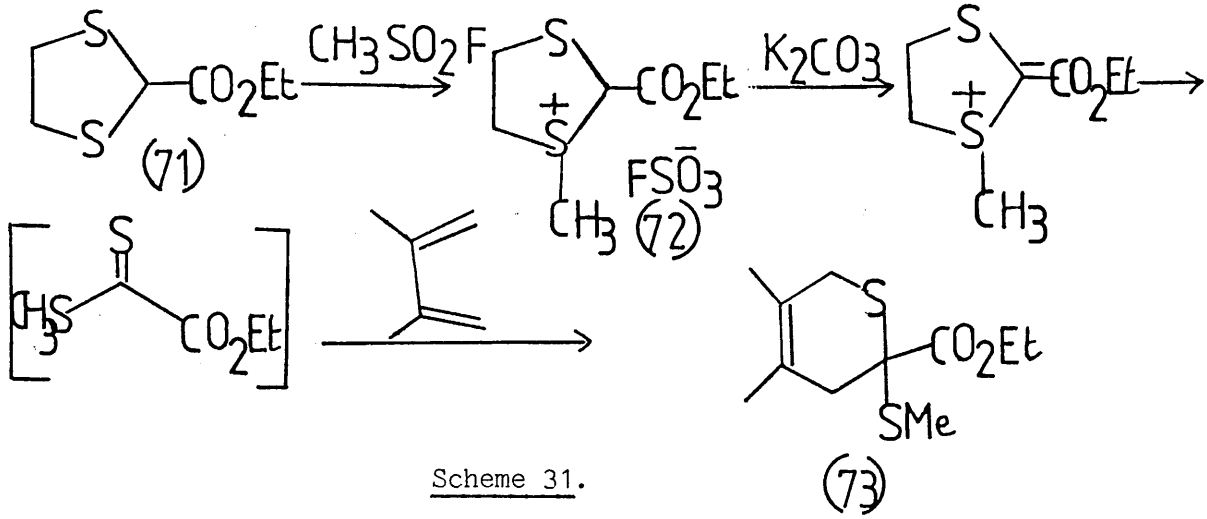
Scheme 29.

-78°C gave a good yield of the cycloadduct (70) (Scheme 30).



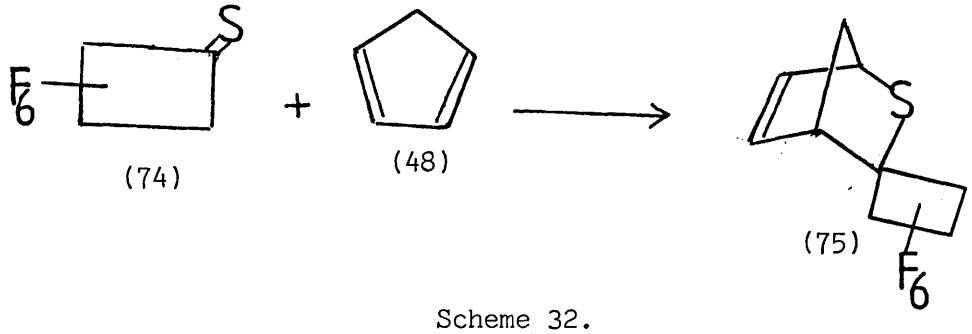
Scheme 30.

An efficient method for producing dithioesters and their cycloadducts was developed by Vedejs et al[38]. They converted 2-ethoxycarbonyl-1,3-dithiolane (71) into the crystalline sulphonium salt (72) with methyl fluorosulphonate. This was then treated with potassium carbonate in the presence of 2,3-dimethyl-1,3-butadiene (41) at 20°C to give the cycloadduct (73) formed, presumably, from an intermediate dithioester. A mechanism is shown in Scheme 31.



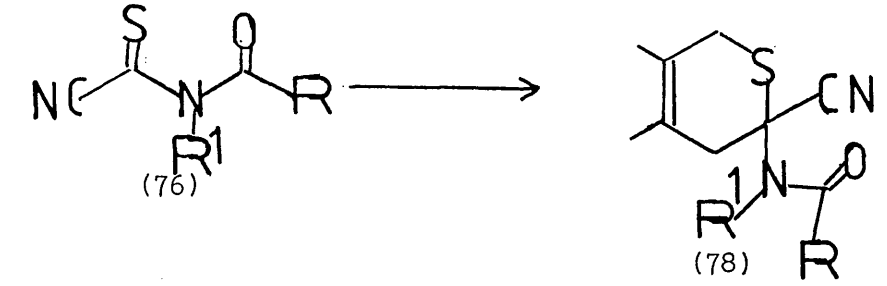
Scheme 31.

The review by Weinreb and Staib[39] in 1982 contains some useful thiocarbonyl compounds employed as dienophiles in Diels-Alder reactions. A spiro-cyclo-adduct[40] (75) was obtained by treating perfluorothiocyclobutanone (74) with cyclopentadiene (Scheme 32). Interesting compounds such as (78) and (79) were obtained in good



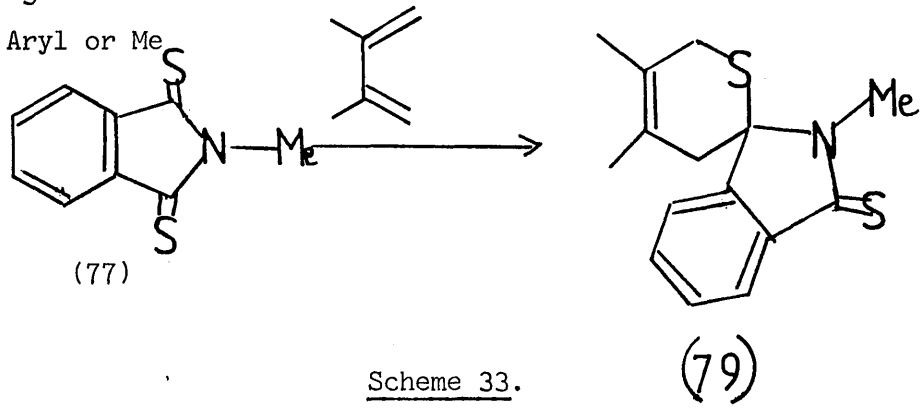
Scheme 32.

yields under mild conditions by treating the cyanothioformamides[41] (76) and the dithiophthalimide[42] (77), respectively with 2,3-dimethyl-1,3-butadiene (Scheme 33).



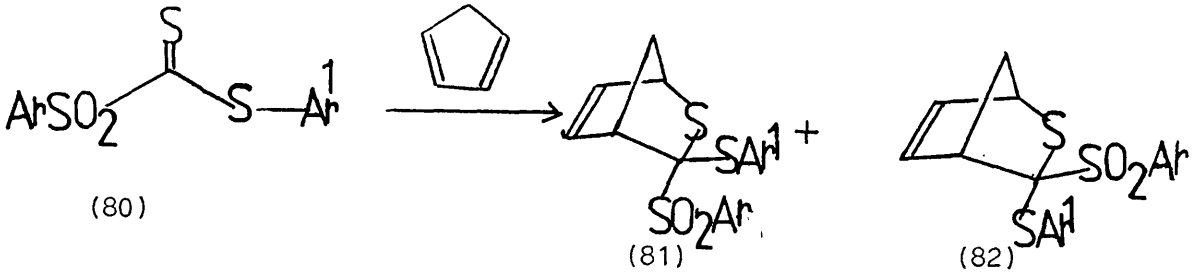
R = CF_3, Me or Ph

R^1 = Aryl or Me



Scheme 33.

Trithiocarbonate S,S-dioxides[43] (80) are reactive dienophiles in Diels-Alder reactions. Thus, their addition to cyclopentadiene gave a 3:1 mixture of the endo- and exo-adducts (81) and (82) (Scheme 34). Similarly, the trithiocarbonate derivative[44]



(80) (81) (82)

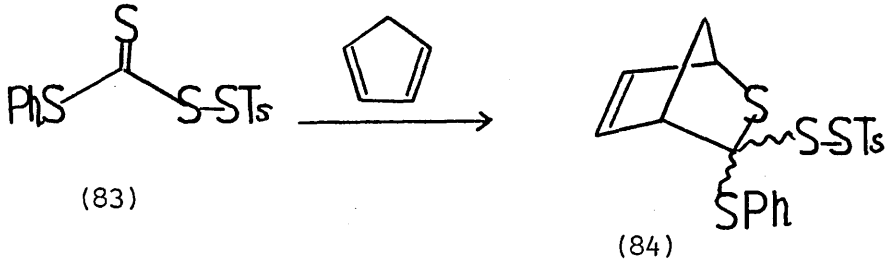
3:1 ratio

Ar = p-tolyl or p-ClC_6H_4

Ar^1 = phenyl or p-ClC_6H_4

Scheme 34.

(83) reacted with cyclopentadiene and afforded the adducts (84) (Scheme 35).

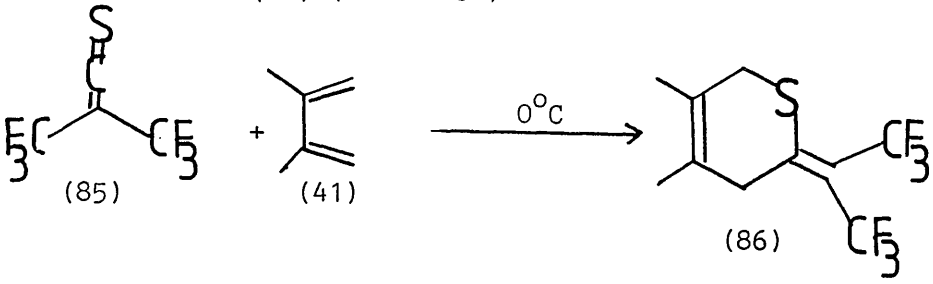


(83) (84)

T_s = 4-$MeC_6H_4SO_2$

Scheme 35.

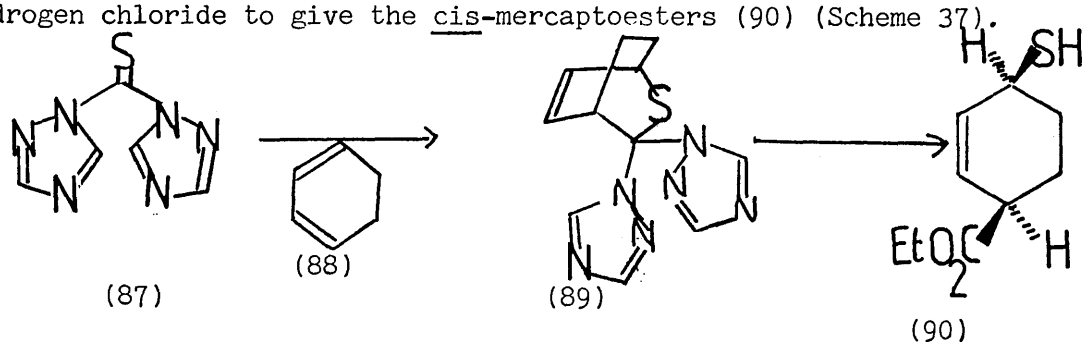
Thioketenes were found to be stable enough to isolate, and had excellent dienophilic properties[45]. Bis-(trifluoromethyl) thioketene (85) reacted with dimethylbutadiene (41) and afforded a good yield of the adduct (86) (Scheme 36).



(85) (41) (86)

Scheme 36.

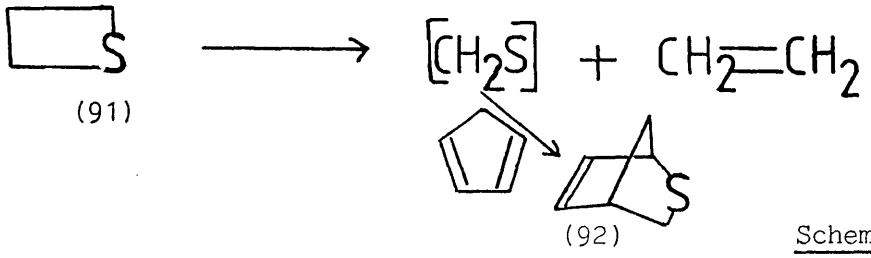
Larson and Harpp[46] reported that the bis-triazole (87) undergoes 1,4-cycloaddition with 1,3-conjugated dienes to give high yield of the cycloadducts. They treated (87) with cyclohexadiene (88) and obtained the adduct (89) which then was treated with ethanolic hydrogen chloride to give the cis-mercaptoesters (90) (Scheme 37).



Scheme 37.

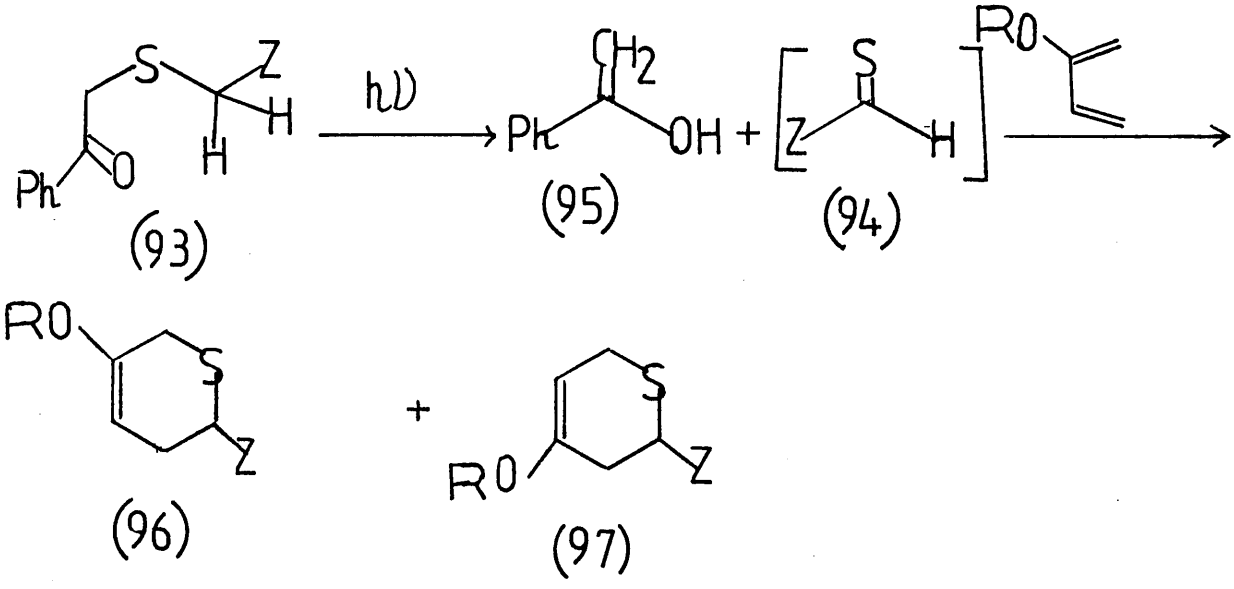
1.4 Cycloaddition Reactions of Thioaldehydes.

Surely, thioaldehyde cycloadditions were entirely neglected until recently because the monomers were almost always too unstable to be isolated. Also, stable thioaldehydes; like the pyrrole derivatives (20) and the very recently described tri-t-butylbenzenethial (36), are stable because they are unreactive, i.e. of little use in synthesis. Therefore the synthetic applications of thioaldehydes depend upon good methods for their generation and trapping in situ with, e.g. conjugated dienes. Photolysis of thiethane (91) in the presence of cyclopentadiene in the vapour phase at temperatures between 25 and 235°C was studied by Dice and Steer.[47] The product (92) clearly arose from the 1,4-cycloaddition of thioformaldehyde to cyclopentadiene. The yield was found to increase with higher pressure of cyclopentadiene (Scheme 38).



Scheme 38.

In 1982, Vedejs and co-workers[48] reported an effective method, based on an earlier observation by Woodward et al[49], for the generation of transient thioaldehydes. The photolysis of phenacyl sulphides (93) afforded, by Norrish cleavage, the transient thioaldehydes (94) and the enol of acetophenone (95). These thioaldehydes were trapped by various 1,3-dienes to give the Diels-Alder adducts (96) and (97), but no cycloadduct of thiobenzaldehyde or thioacrolein was obtained (Scheme 39). The major adducts (96) were found to be those with sulphur attached to the more electron-rich

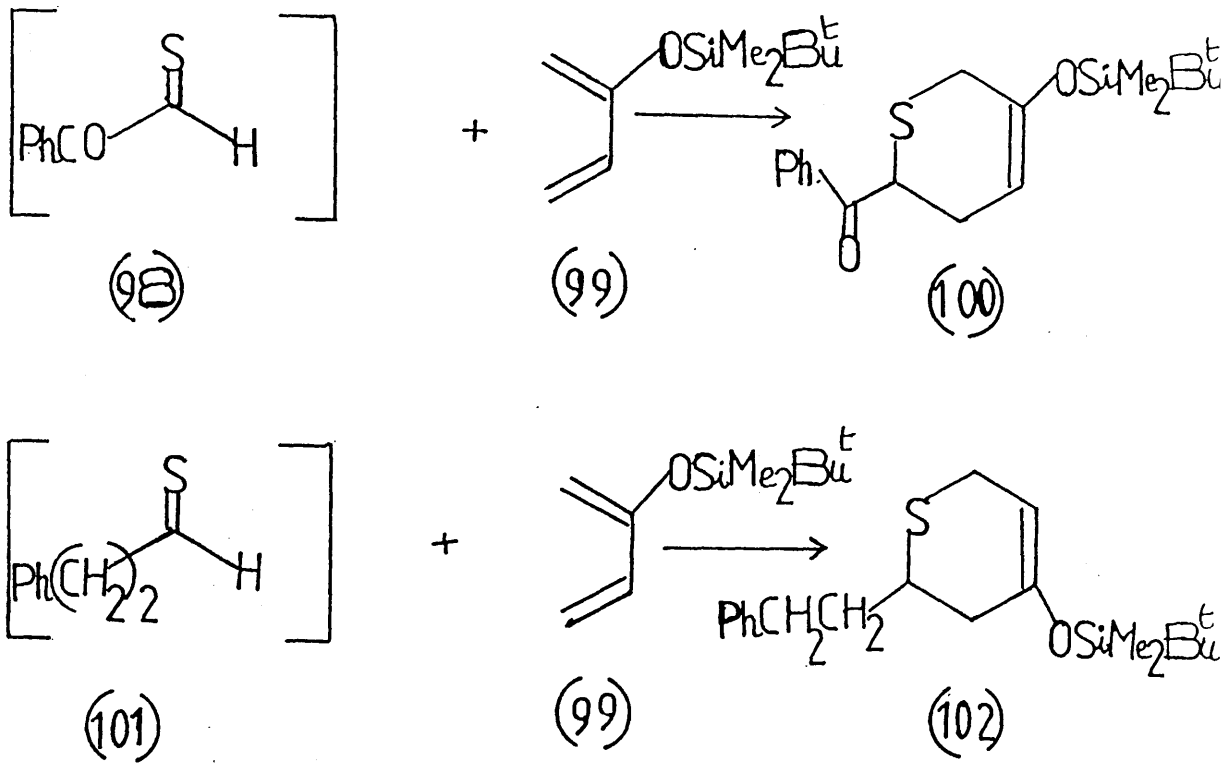


Scheme 39.

end of the diene. This result is in agreement with the previous work on dithioesters[38], but with less selectivity. This was thought to be due to the greater reactivity of thioaldehydes. Recently Vedejs et al[50], following their earlier observations, reported an extensive study on Diels-Alder trapping of the photochemically generated thioaldehydes, one class with electron-withdrawing groups, and the other class with electron-donating groups. It was found that the first class reacts efficiently with 2-substituted 1,3-conjugated dienes, especially with cisoid or donor-substituted dienes, whereas the second class requires an excess of the 2-substituted

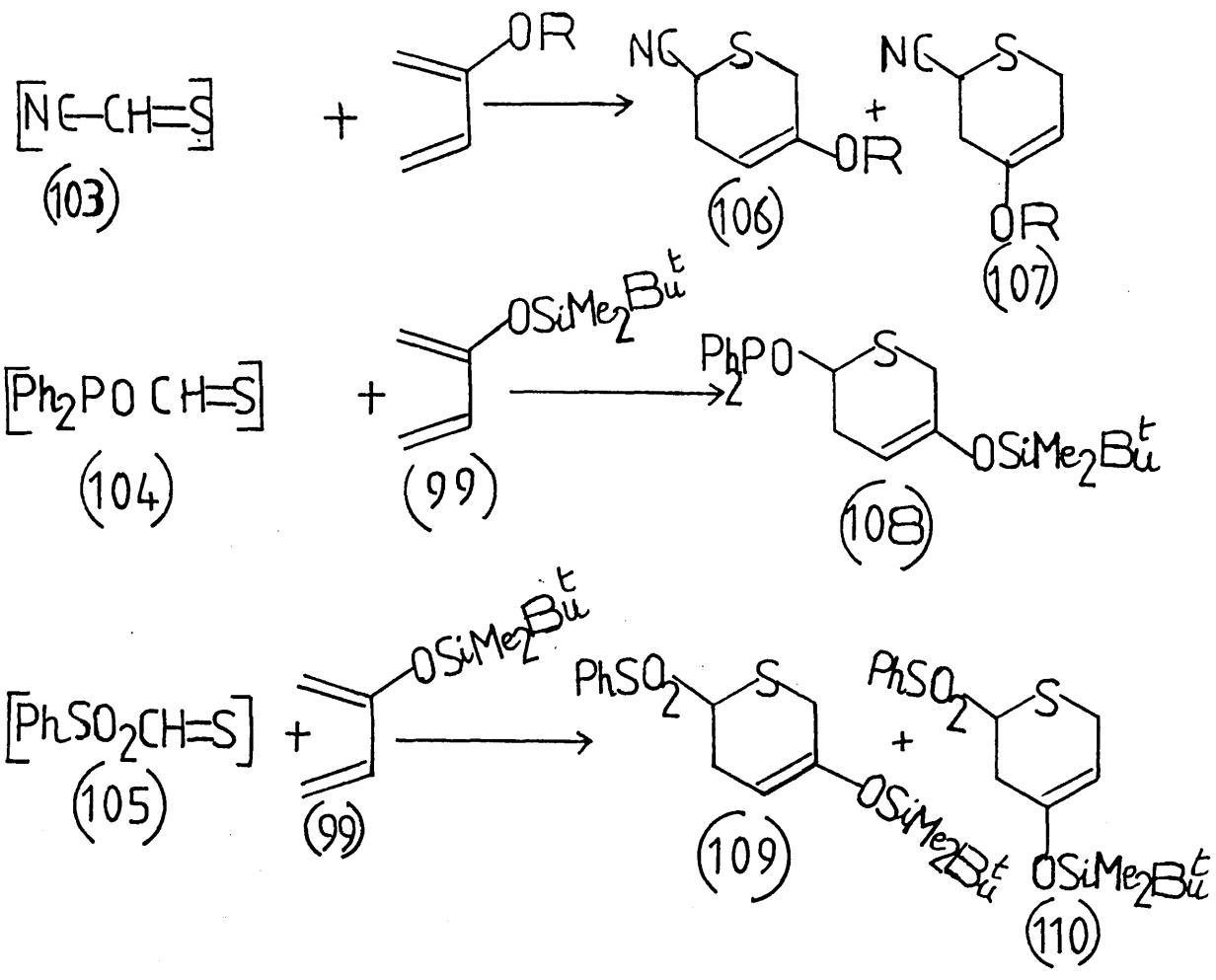
1,3-dienes to react reasonably efficiently. The regiochemistry of the two series was found to be the reverse of each other. Thus, the thioaldehyde (98) having an electron-withdrawing group, PhCO, reacted with the diene (99) to give mainly the cycloadduct (100) (Scheme 40).

In contrast, the thioaldehyde (101) lacking an electron-withdrawing group gave



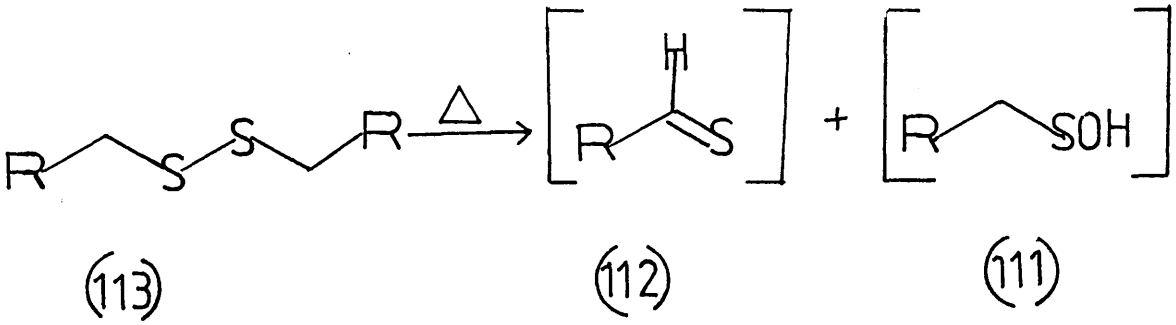
Scheme 40.

exclusively the cycloadduct (102) of opposite regiochemistry. The photochemical method for generating thioaldehydes was extended to include examples such as NCCHS (103), Ph_2POCHS (104), and $PhSO_2CHS$ (105). These were trapped by various dienes to give Diels-Alder adducts, which are shown in Scheme 41. As expected, since all these new types of thioaldehydes had electron-withdrawing groups, the major regioisomers (106), (108), and (109) corresponded to that of (100) formed from the benzoyl derivative (98).

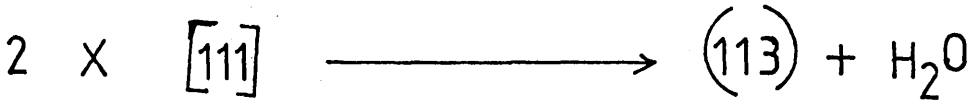


Scheme 41.

Baldwin and Lopez[51] reported a useful non-photochemical method for the generation and trapping of thioaldehydes. This method (Scheme 42) was first discovered by Block et al[52,53]. However, they trapped the sulphenic acids(111) with acetylenes, but did not trap the thioaldehyde (112). Baldwin and Lopez showed that thermolysis of symmetrical alkyl thiosulphinates (113) afforded the thioaldehyde (112) and the sulphenic acids (111). The recombination of two molecules of (111) with elimination of water gave the starting material (Scheme 42). Thus eventually all the thiosulphinates were converted into the thioaldehydes (112). The thioaldehydes generated by this method were



(113) (112) (111)

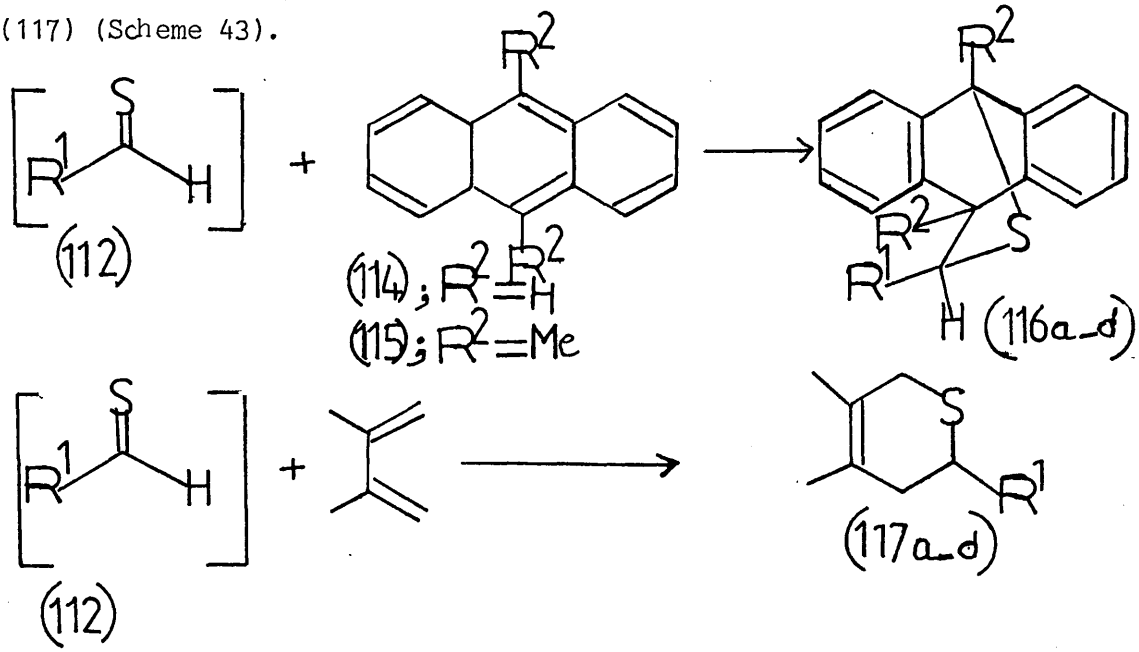


a; R = Me

b; R = Ph

Scheme 42.

trapped efficiently by a variety of symmetrical 1,3-conjugated dienes such as anthracene(114), 9,10-dimethylanthracene(115), and 2,3-dimethyl-butadiene (41) to give the corresponding Diels-Alder adducts (116) and (117) (Scheme 43).



a; R^1 = Me, R^2 = H

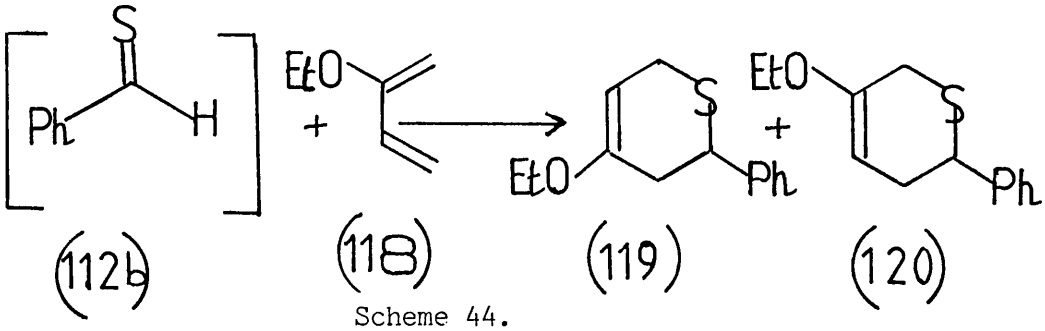
b; R^1 = Ph, R^2 = H

c; R^1 = Me, R^2 = Me

d; R^1 = Ph, R^2 = Me

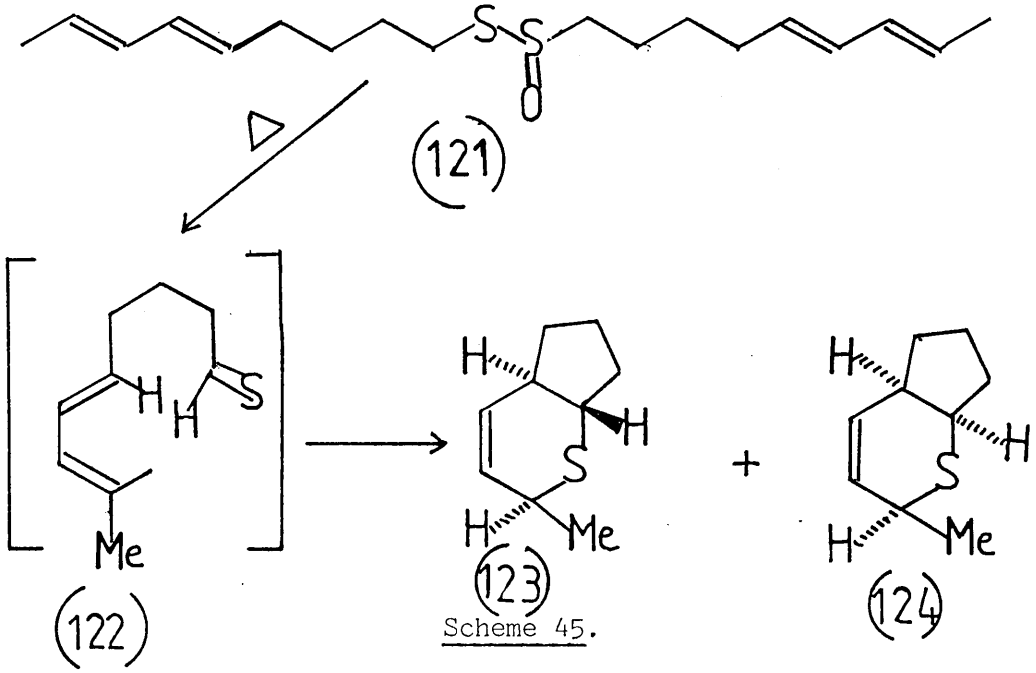
Scheme 43.

The anthracene(116b) was found to be an efficient and clean source of thiobenzaldehyde. Heating the adduct (116b) with 2,3-dimethylbutadiene in toluene gave the adduct (117b) in good yield. Similarly, thiobenzaldehyde (112b) was trapped by the unsymmetrical 2-ethoxy-1,3-butadiene (118) to give the adducts (119) and (120) (Scheme 44). The regioselectivity in this reaction was not as great



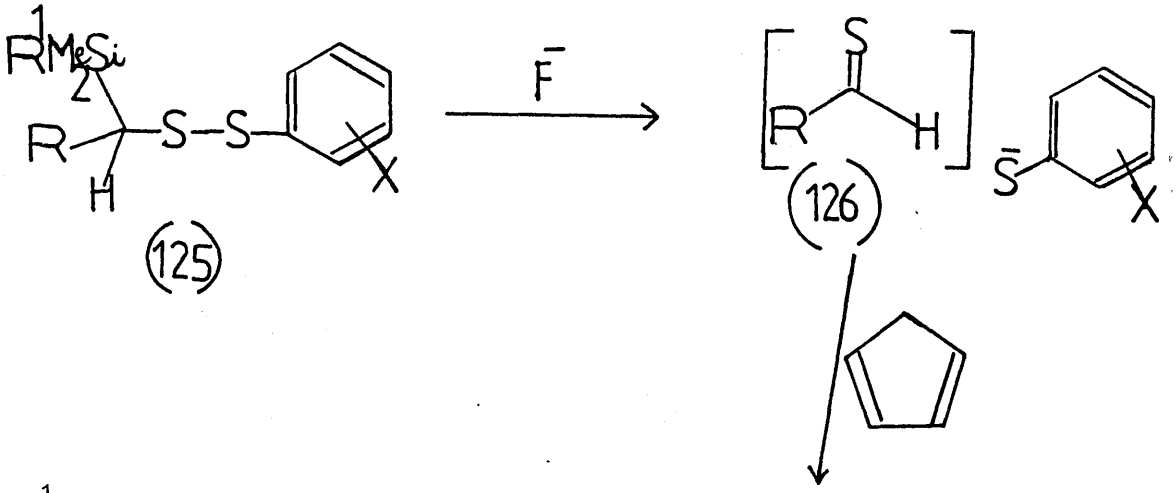
Scheme 44.

as had been observed for the strongly electron-deficient thio-aldehydes[50], although the isomer (119) was the major product suggesting that the phenyl group had acted as a weakly electron-donating group. Using the same method, the first intramolecular Diels-Alder reactions of thioaldehydes were performed successfully by the same workers[51]. The thermolysis of thiosulphinate (121) gave the transient thioaldehyde (122) which then cyclised to give the adducts (123) and (124) in a ratio of 1:1 (Scheme 45).



Scheme 45.

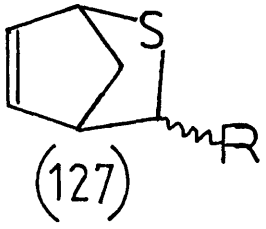
An efficient and practical method for generation of thioaldehydes from α-silyldisulphides was reported by Krafft and Meinke[54] (scheme 46). The precursors (125) were prepared from the corresponding aldehydes, RCHO, or thiols, $ArCH_2SH$. Efficient trapping of the thioaldehydes by cyclopentadiene was observed when the precursors (125) were cleaved by caesium or tetrabutylammonium fluoride at 0 - 25°C.



R^1 = Me, Ph

X = 4-Cl or 2-NO_2

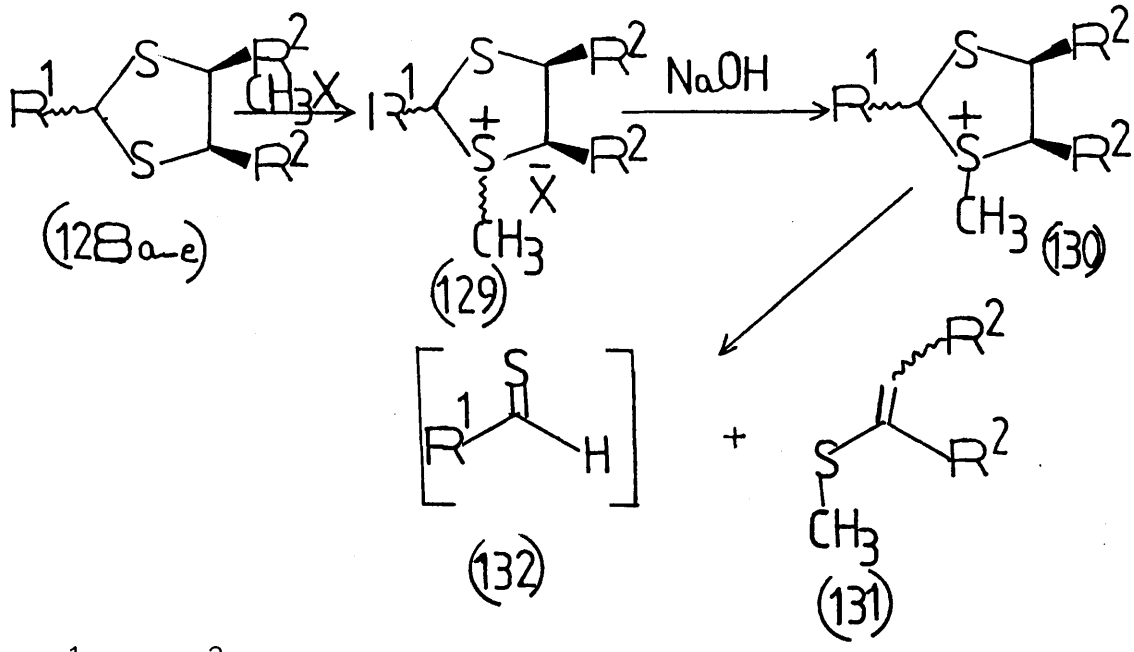
R = H, Me, Et, n-Pr, n-Bu
i-Pr, Ph, $PhCH_2$, or cyclohexyl



Scheme 46.

Another convenient method for the generation of thioaldehydes under mild conditions was reported by Schauman and Ruhter[55]. The thioaldehyde precursors (129) can be deprotonated selectively when they are substituted with electron-withdrawing groups, or a phenyl group in the 4 and 5 positions. The dithiolanes (128a-d) were treated with methyl fluorosulphonate, and the dithiolane (128e) with trimethyloxonium tetrafluoroborate, to give the corresponding sulphonium salts (129). Deprotonation of (129) with sodium hydride gave the ylides (130), which underwent spontaneous fragmentation to

give the vinyl sulphides (131) and the thioaldehydes (132) (Scheme 47). The thioaldehyde (132; R^1 = Bu^t) was trapped by benzylideneaniline N-oxide (133) to give the adduct (134),



a; R^1 = Me, R^2 = Co_2Me

b; R^1 = Bu^t, R^2 = Co_2Me

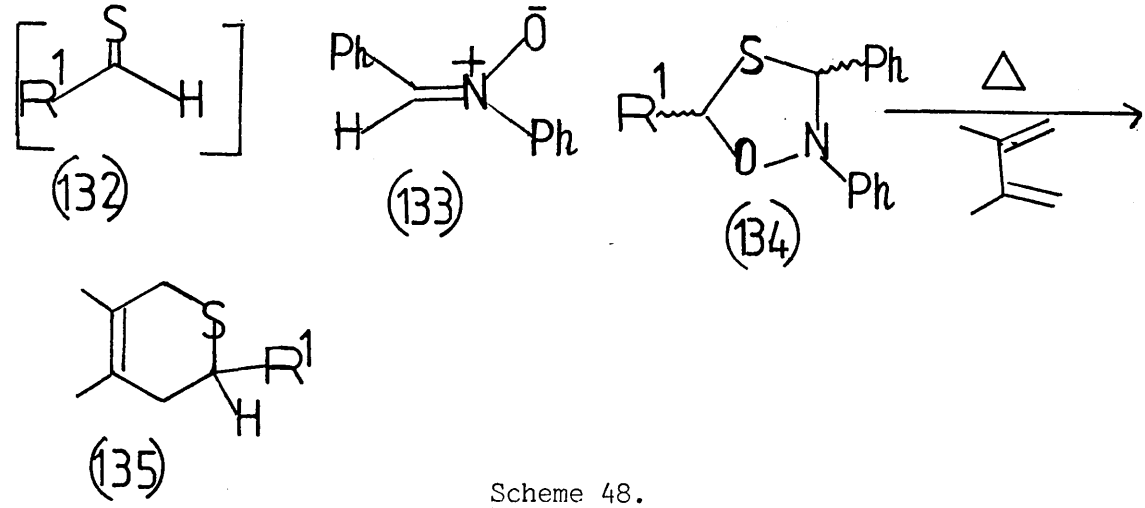
c; R^1 = Ph, R^2 = Co_2Me

d; R^1 = H_2C=CH, R^2 = Co_2Me

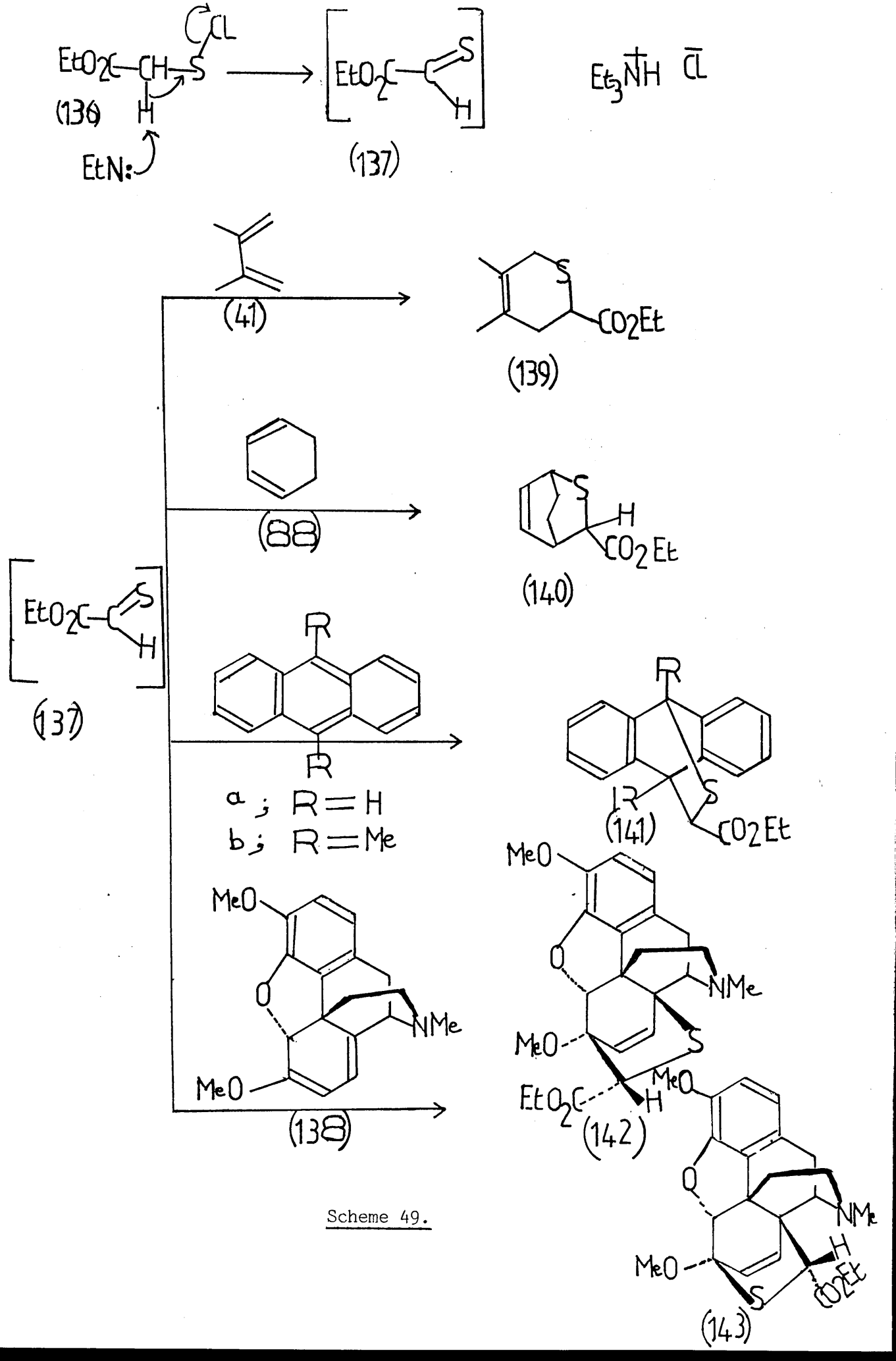
e; R^1 = Bu^t, R^2 = Ph

Scheme 47.

which, on being heated in toluene in the presence of 2,3-dimethyl-butadiene, gave the Diels-Alder adduct (135) in 39% yield (Scheme 48).

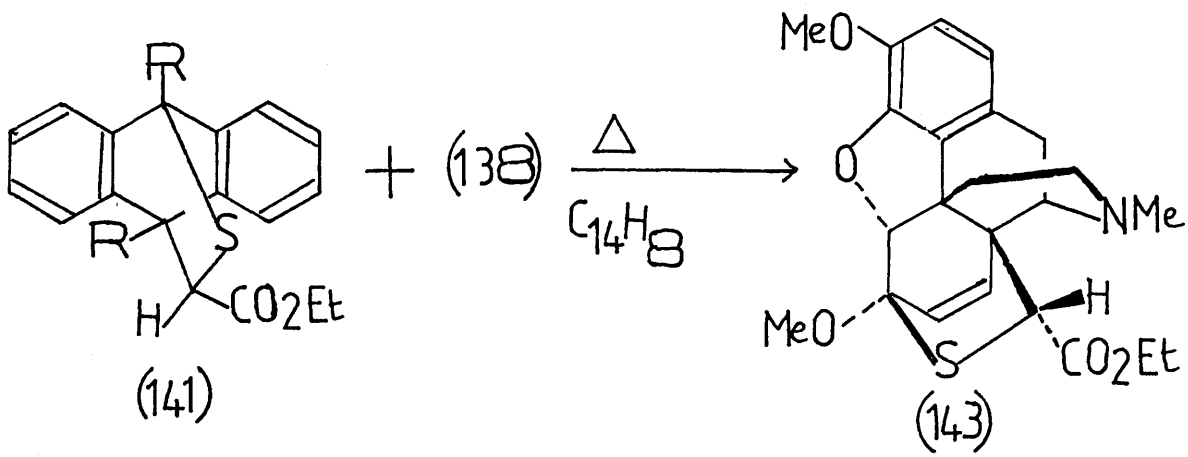


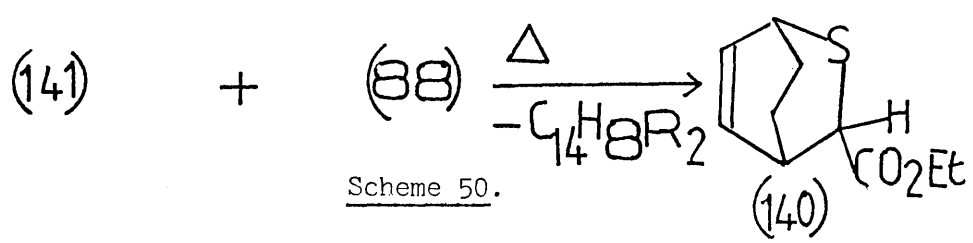
Scheme 48.



Scheme 49.

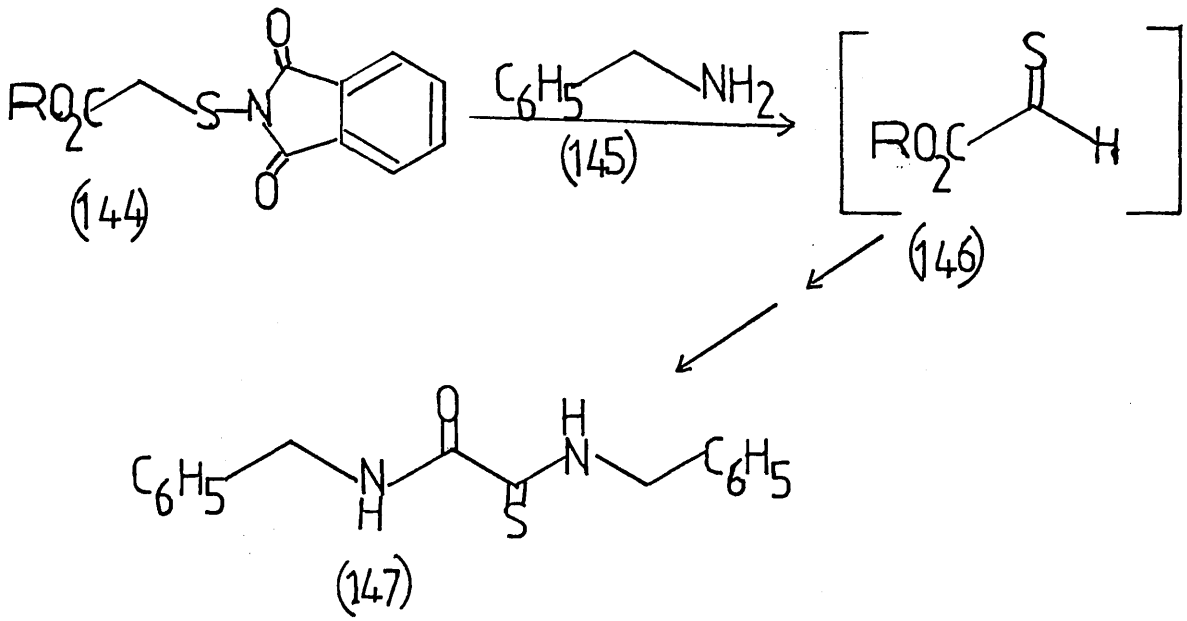
In 1983 Kirby and co-workers[56] reported the formation of ethyl thioxoacetate (137) from the sulphenyl chloride (136) by elimination of hydrogen chloride with triethylamine. The thioaldehyde (137) was trapped by a variety of 1,3-dienes such as 2,3-dimethylbutadiene, cyclohexadiene, anthracene, 9,10-dimethylanthracene and the alkaloid thebaine (138) to give the adducts (139), (140), (141), and (142) and (143) (Scheme 49). The major thebaine adduct (142) was found to be unstable, when it was heated under reflux in toluene for 8h it was converted in high yield into the isomer (143), indicating that (142) had been formed under kinetic control. Also, the anthracene and dimethylanthracene adducts (141 ; R = H) and (141 ; R = Me) were found to be clean sources of ethyl thioxoacetate. Thus, when the adduct (141 ; R = Me) was heated in toluene with an equimolar amount of thebaine (138) at 100°C for 10h, the adduct (143) was obtained in 78% yield. Similarly, the adduct (141 ; R = H) and thebaine gave (143) in 86% yield after 5h at 110°C. Finally, the adduct (140) was obtained in 79% yield after heating 1,3-cyclohexadiene and the adduct (141 ; R = H) for 3h at 110°C (Scheme 50).





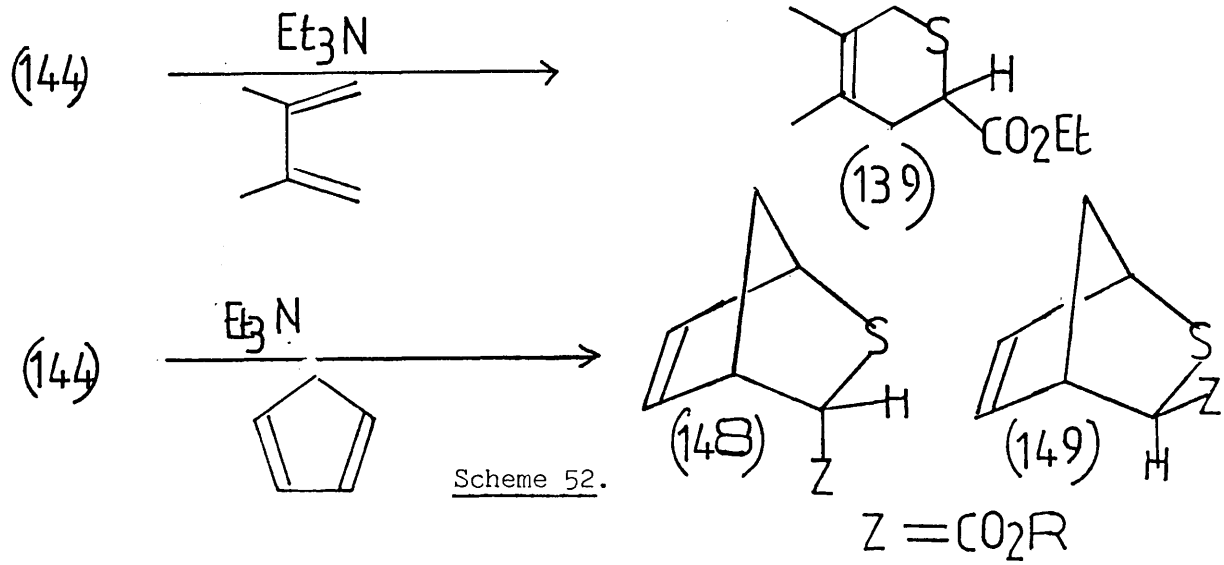
Scheme 50.

Harpp and Bock[57] found that treatment of the N-thiophthalimide (144 ; R = Me) with benzylamine (145) gave the thioxamide (147) in low yield. It was suggested that the compound (147) was formed in a complex manner from the thioaldehyde (146) generated by base catalysed elimination of phthalimide from the precursor (144) (Scheme 51). Kirby and Lochead[58] investigated this reaction further. They



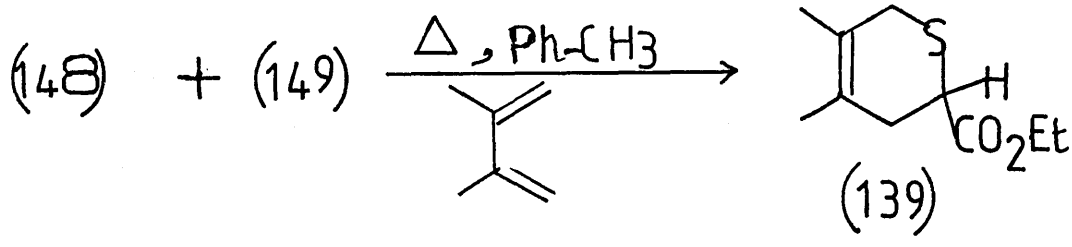
Scheme 51.

treated the N-thiophthalimides (144 ; R = Me or Et) with triethylamine in the presence of 2,3-dimethylbutadiene and obtained the corresponding cycloadducts (139). Similarly, cyclopentadiene cycloadducts (148) and (149) were obtained in high yield in the endo : exo ratio, 7 : 3 (scheme 52).



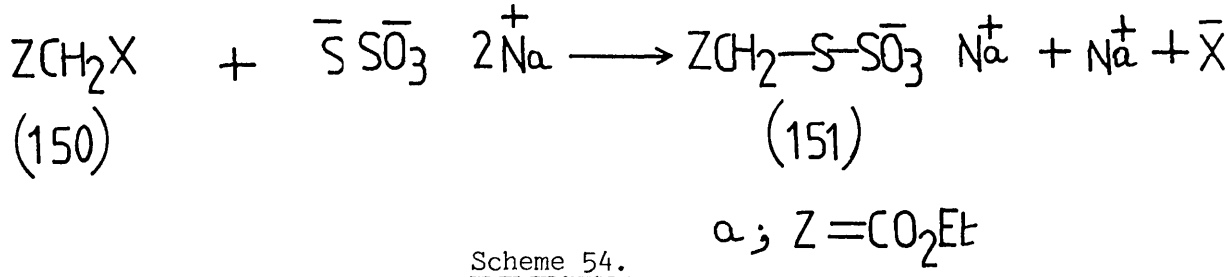
Scheme 52.

The same workers[58] heated the kinetically determined mixture of (148) (70%) and (149) (30%), or each isomer separately in toluene under reflux for 7h and obtained the same equilibrium mixture of (148) (30%) and (149) (70%). This suggested that the cyclopentadiene cycloadducts might be good precursors of the thioaldehyde for synthetic purposes. Thus, when the kinetic mixture of (148) and (149) was heated with 2,3-dimethylbutadiene in toluene under nitrogen at 120°C for 12h the cycloadduct (139) was obtained in 82% yield (Scheme 53).



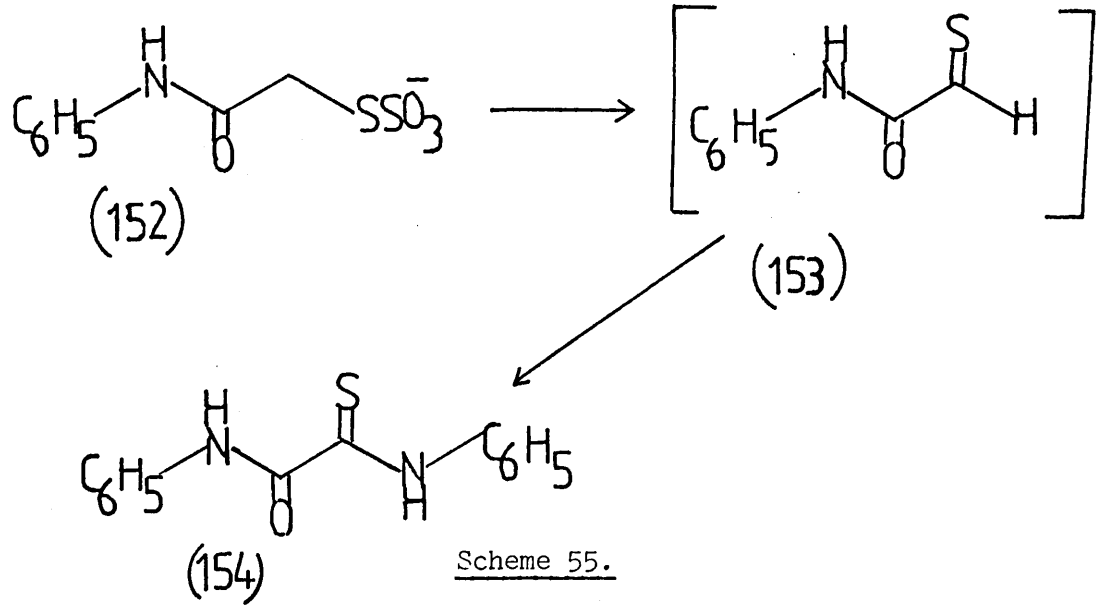
Scheme 53.

The sulphenyl chlorides (136) were prepared by treating the corresponding thiols with N-chlorosuccinimide and the N-thiophthalimides (144) were prepared from the corresponding disulphides and N-bromophthalimide, by the method of Buchel and Conte.[59] However, it was desirable to have simple routes to thioaldehyde precursors from sulphur free starting materials. Therefore to extend the scope and to improve the synthetic convenience of this general route to thioaldehydes, a new series of precursors (150 ; X = SO_3Na, Z = EtO_2C, PhNHCO, NC, or 4-$NO_2C_6H_4$) was studied[60]. These precursors are 'Bunte salts' (151), readily available from simple alkyl halides (150) by treatment with sodium thiosulphate (Scheme 54). These thiosulphate S-esters were first described by the German chemist Hans Bunte[61].



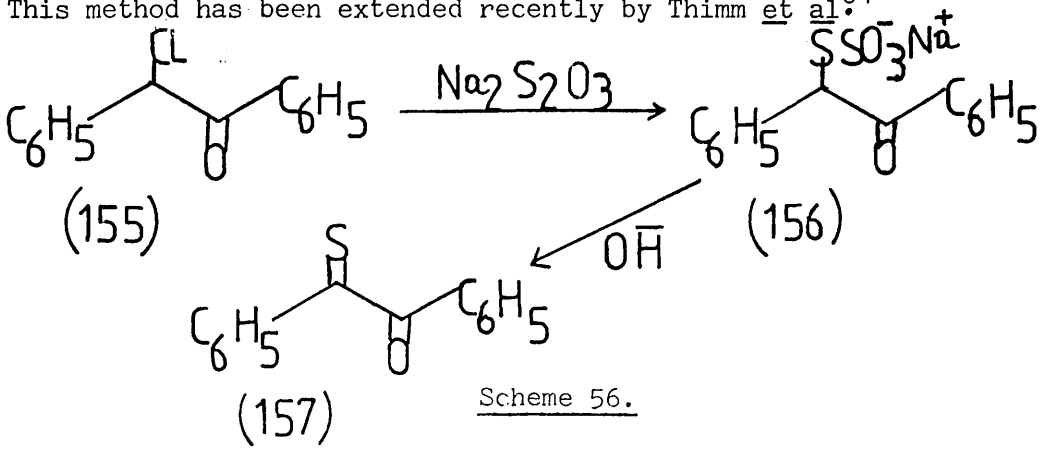
Scheme 54.

More recently, Milligan and Swan[62] studied the reactions of these salts with primary and secondary amines. Thus, treatment of the Bunte salt (152) with aniline gave the thio-oxamide (154). They discussed possible mechanisms and suggested that the first step involved elimination of sulphite to give the thioaldehyde (153) (Scheme 55). Saville and Steer[63] reported that desyl Bunte salt (156).



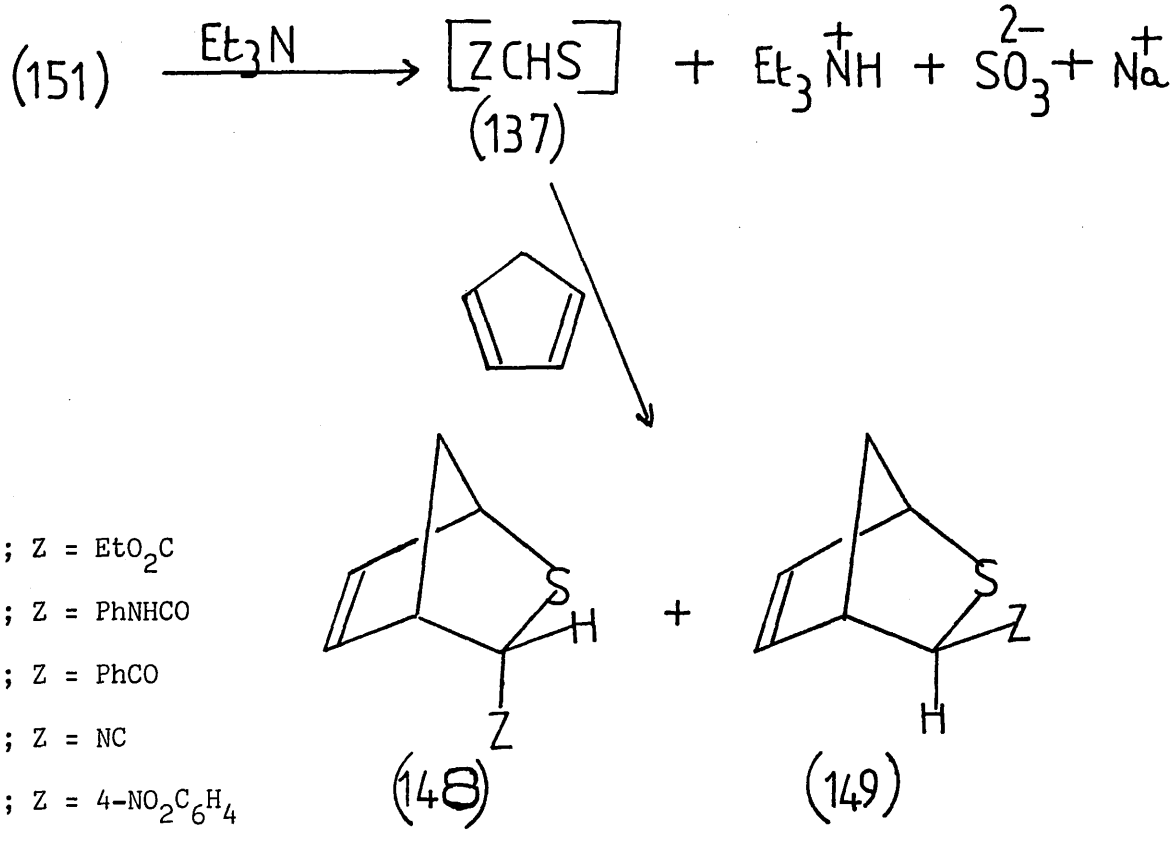
Scheme 55.

prepared from desyl chloride (155) and sodium thiosulphite, gave monothiobenzil (157) when treated with sodium hydroxide (Scheme 56). This method has been extended recently by Thimm et al.[64]



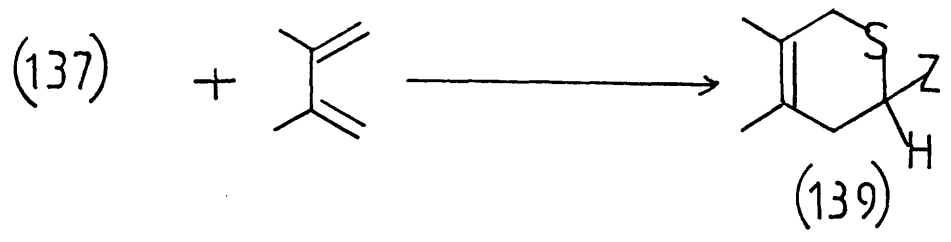
Scheme 56.

These observations encouraged Kirby et al[60] to study the elimination reaction of the Bunte salt (151 ; Z = EtO_2C) in the presence of conjugated dienes in the hope of trapping the thioaldehyde (137). Treatment of the Bunte salt (151 ; Z = EtO_2C) with triethylamine in the presence of cyclopentadiene and calcium chloride dihydrate gave high yields of the adducts (148a-e) and (149a-e) (Scheme 57). The same thioaldehydes (137) were also trapped by the



Scheme 57

less reactive 2,3-dimethylbutadiene to give reasonable yields of the desired adducts (139a-e) (Scheme 58). Calcium chloride



Scheme 58

dihydrate was added to the reaction mixture to remove the nucleophilic sulphite dianion either by precipitation or ion-pairing, otherwise, the cycloadducts were obtained in low yields and water soluble by-products were formed, perhaps by attack of the sulphite dianion on the thioaldehyde carbon.

Following the work on Bunte salts, another class of thioaldehyde precursors was studied[65]. It was thought that the thiotosylates (158 ; Tol = 4-MeC_6H_4) would behave similarly to the Bunte salts (151), moreover, their singly charged leaving group, $TolSO_2^-$, would be expelled more readily (Scheme 59).

$$\underset{(158)}{RCH_2SSO_2Tol} + Et_3N \longrightarrow \underset{(137)}{[RCHS]} + Et_3\overset{+}{N}H + TolSO_2^-$$

Scheme 59.

It was found, unexpectedly, that the thiotosylates (158) were readily transformed into the α-sulphonyldisulphides (159) (Scheme 60). The tosyldisulphides (159) were also found to be, unexpectedly, good

$$\underset{(158)}{2RCHSSO_2Tol} \longrightarrow \underset{(159)}{RCH_2SSCH(SO_2Tol)R} + TolSO_2H$$

a; R = 4-$NO_2C_6H_4$

b; R = Ph

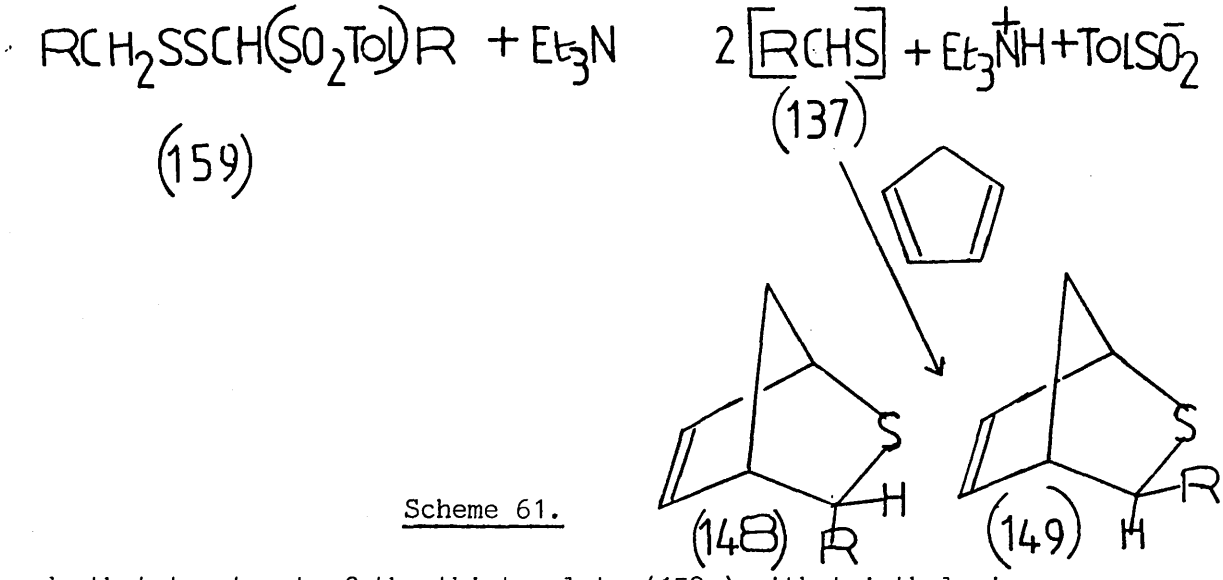
c; R = 4-BrC_6H_4CO

d; R = EtO_2C

Scheme 60.

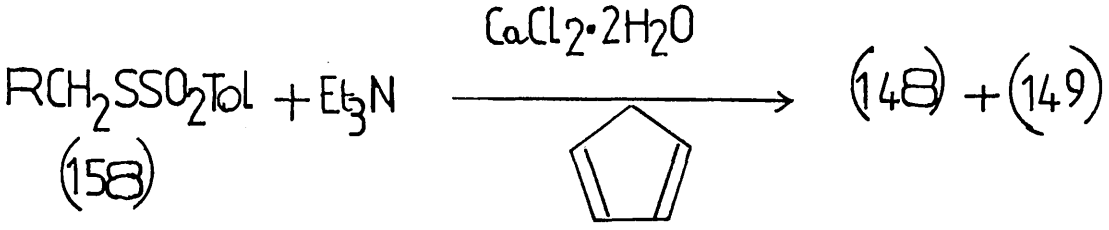
thiolaldehyde precursors. Thus, when the tosyldisulphides (159a), (159c), and (159d) were treated with triethylamine in the presence of

2 mol equivalents of cyclopentadiene in benzene at room temperature, the corresponding adducts (148) and (149) were formed. The observed endo : exo ratios were 7 : 1(a), 7 : 4 (c) and 7 : 3 (d). The benzyl derivative (159b) was much less reactive; nevertheless, with triethylamine and cyclopentadiene in acetonitrile it gave the adducts (148b) and (149b) in a ratio of 4 : 1 (Scheme 61). It was



Scheme 61.

found, that treatment of the thiotosylate (158a) with triethylamine in the presence of cyclopentadiene and calcium chloride dihydrate at room temperature gave the adducts (148a) and (149a) in 82% yield (Scheme 62). Whereas, when the same reaction was carried out in



Scheme 62.

the absence of calcium chloride dihydrate the disulphide (159a) was the major product. It was proposed that the toluene p-sulphinate anion is removed by the calcium cation, by either precipitation or ion-pairing. This confirmed the suggestion that the α-sulphonyldisulphides (159) arise by attack of toluene p-sulphinate on the initially formed thioaldehydes.

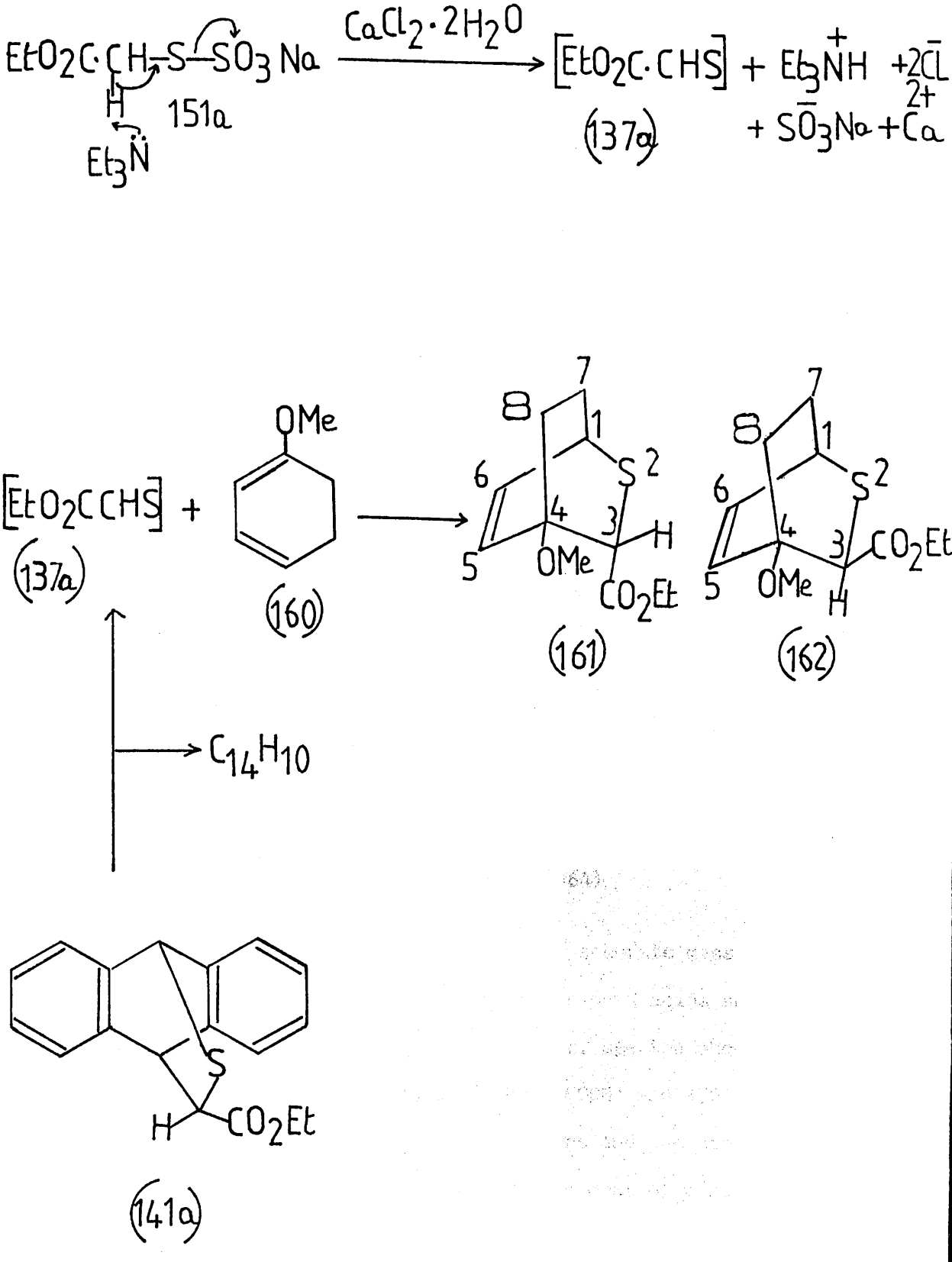
CHAPTER TWO

DISCUSSION

2.1 Cycloaddition of Ethyl Thioxoacetate and 1-Methoxy-1,3-Cyclohexadiene.

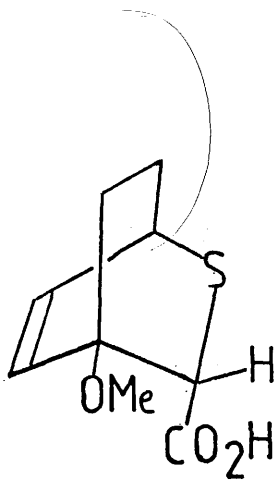
The use of Bunte salts, for example the ethyl ester (151a), as precursors of thioaldehydes, e.g. ethyl thioxoacetate (137a), was described in Chapter 1. This early work generally employed symmetrical dienes as trapping agents, the one exception being thebaine(138). The aim of the present study was to explore the regiochemistry and stereochemistry of the reaction of thioxoacetate esters with unsymmetrical conjugated dienes.

The first of these studied was 1-methoxy-1,3-cyclohexadiene, a close analogue of thebaine. Accordingly, when the Bunte salt (151a) was treated in ethanol-benzene at room temperature with equimolecular amounts of triethylamine and calcium chloride dihydrate, in the presence of one mol equivalent of 1-methoxy-1,3-cyclohexadiene (160), the cycloadducts (161) and (162) were obtained in 57% yield after 5 days (Scheme 63). The endo:exo ratio was 4:1 as judged from integration of the olefinic signals in the ^{1}H n.m.r spectrum of the reaction mixture. The two isomers were separated on preparative silica t.l.c. plates and were obtained in approximately the same ratio as determined by integration of the ^{1}H n.m.r. spectrum. The same esters (161) and (162) were obtained using the alternative method for generating ethyl thioxoacetate, that is by thermal dissociation of the anthracene adduct (141a). Thus, the anthracene adduct (141a) was heated under reflux in toluene with 1-methoxy-1,3-cyclohexadiene (1.3 mol equiv.) for 4h, by which time all the anthracene adduct had decomposed. The cycloadducts (161) and (162) were isolated in a combined yield of 67.5% and in essentially the same endo:exo ratio of 4:1.

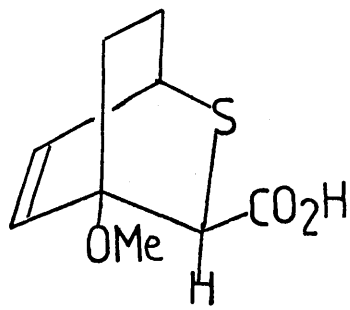

EtO2C·CH2·S·SO3Na
H
Et3N
151a
CaCl2·2H2O
[EtO2C·CHS]
(137a)
+ Et3NH
+ SO3Na
+ 2Cl
Ca2+
[EtO2CCHS]
(137a)
OMe
(160)
C14H10
(161)
(162)
CO2Et
OMe
H
S
(141a)

Scheme 63.

The molecular formula of the adducts (161) and (162) was determined by accurate mass measurement. The fragmentation patterns were also useful and had some points of interest which are discussed in Chapter 3,(Table 3). The presence of the carbonyl groups was indicated by i.r. spectroscopy ν_{max} 1735 cm^{-1}. When the esters (161) and (162) were hydrolysed with 1.03M sodium hydroxide in tetrahydrofuran at room temperature the crystalline acids (163) and (164) were obtained in excellent yields, m.p. 114-115°C and 124-125°C respectively. Microanalysis supported the expected elemental



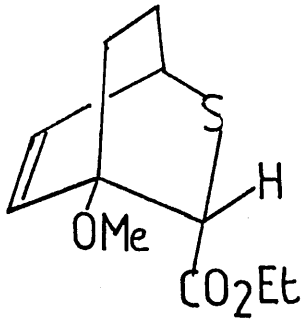
(163)



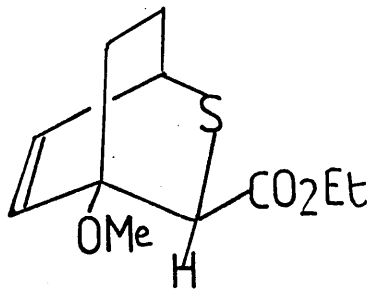
(164)

composition, $C_9H_{12}O_3S$. Mass spectroscopy with accurate mass measurement, confirmed this molecular formula for both acids and gave useful fragments (Chapter 3, Table 4). The i.r. spectra showed carboxyl carbonyl bands at ν_{max} 1715 cm^{-1} (endo-COOH) and 1705 cm^{-1} (exo-COOH). The ^1H n.m.r. spectra of the esters and the corresponding acids were closely similar, apart from the replacement of ethoxyl signals by broad hydroxyl signals.

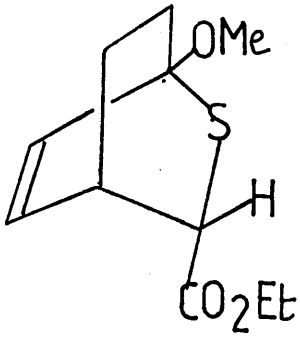
Theoretically, four possible cycloadducts (161) and (162), and (165) and (166), can be formed from the addition of thioxoacetate (137a) to the unsymmetrical 1-methoxy-1,3-cyclohexadiene (160) (Scheme 64).



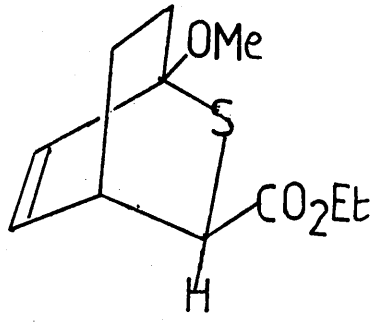
(161)



(162)



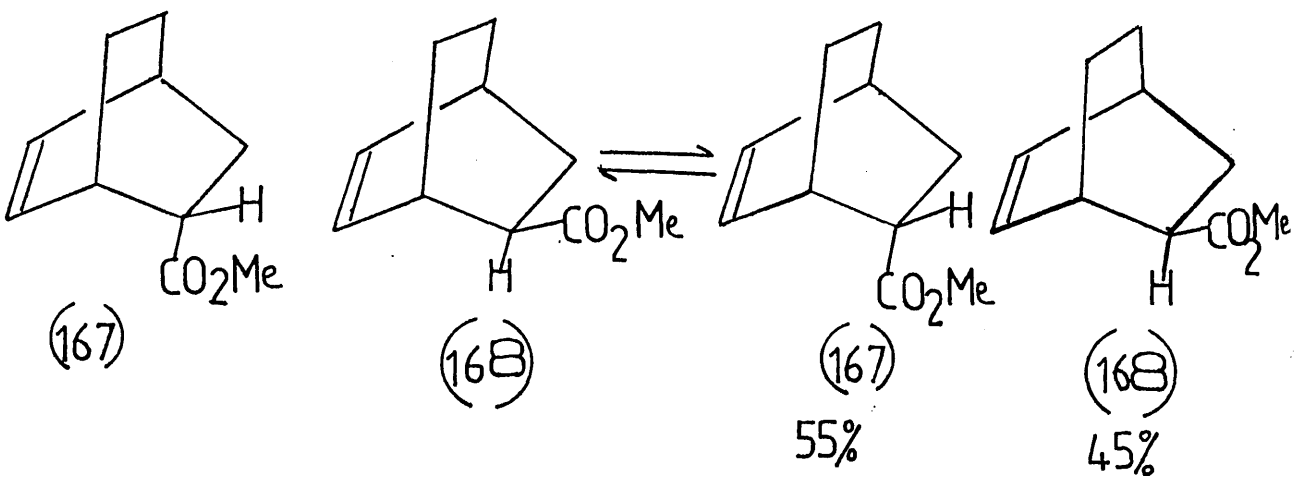
(165)



(166)

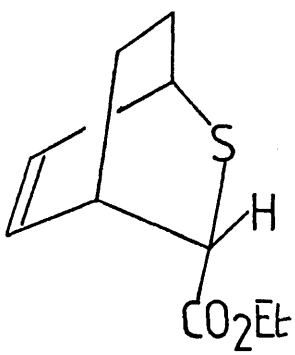
Scheme 64.

These adducts are two pairs of stereoisomers, the members of each pair being interconvertible, in principle, by epimerisation at C(3). We have shown the products to be (161) and (162) for the following reasons. First of all, when Oullette and Booth[66] used base-catalysed epimerisation as an alternative method for confirming the relative stereochemistry of the esters (167) and (168) obtained from methyl acrylate (169) and cyclohexadiene, the ratio of isomers at equilibrium was endo:exo, 55:45. Using the procedure reported by Oullette and

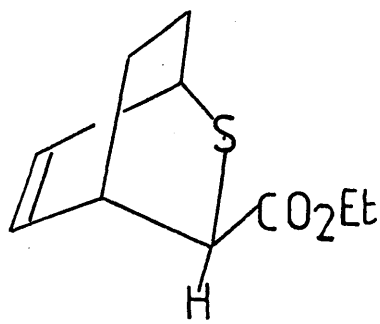


Booth, the major ester (161), prepared from the pure acid (163), was heated under reflux in 0.1M sodium ethoxide for 1h. The resulting mixture contained 40% of the minor ester (162). The minor ester was isolated and hydrolysed to the crystalline acid to establish its identity beyond doubt. To confirm that the reaction had reached equilibrium, the mixture of the esters (161) and (162) (4:1) was heated in sodium ethoxide for 24h. The proportion of the minor isomer was again 40%. The possibility that dissociation and

recombination of the cycloadducts had occurred was excluded by heating the ester (161) in ethanol under reflux for 1h. The ester (161) was unchanged. Our results were essentially in agreement with those obtained by Oullette and Booth, who established the stereochemistry of their endo (major) acid by iodolactonisation. This interconversion of the isomeric esters by epimerisation shows that they indeed have the same regiochemistry. The regiochemistry and stereochemistry of the isomers (161) and (162), and the derived acids (163) and (164), was confirmed by ^{1}H n.m.r. spectroscopy, aided by comparison with the corresponding cycloadducts (140a) and (140b) of cyclohexadiene. The multiplicities of the signals for 3-H were particularly informative. The spectrum of the acid (163) derived from the major ester (161)



(140a)

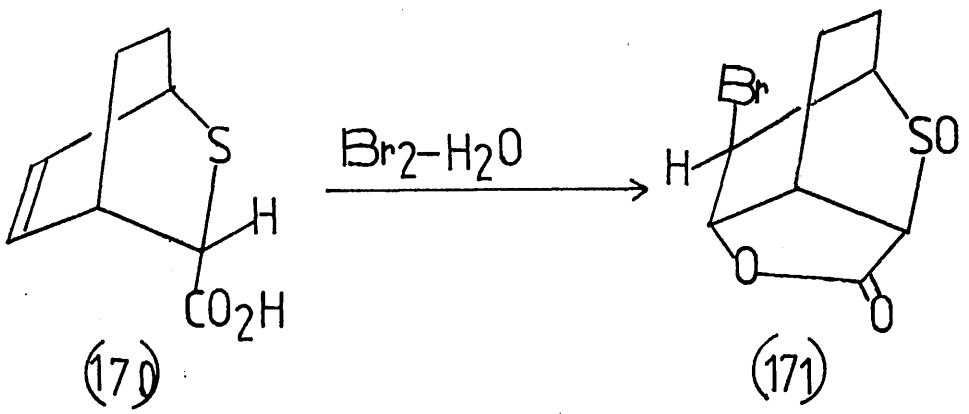


(140b)

showed only a fine-split doublet, J 0.8Hz, for 3-H, whereas the vicinal coupling constants for the cyclohexadiene adducts were $J_{2,3}$ 3Hz (endo) and $J_{2,3}$ 2Hz (exo). Clearly, the major product (161) must have the methoxy group at C(4), and the small splitting (0.8Hz) must arise from long-range coupling. The spectrum of the minor product acid (164) showed a doublet, J 2.2Hz, for 3-H whereas that of the exo cycloadduct of cyclohexadiene (140b) showed a triplet, J.2.1Hz. In both

compounds, there must be a long-range, '(W)' coupling between the endo 3-H and a proton in the ethano bridge. Now, the major isomer (161) and the minor isomer (162) can be called endo and exo respectively. The chemical shifts for protons in 1-methoxy-1,3-cyclohexadiene adducts were similar to those of the parent adducts.

The stereochemistry of the endo cyclohexadiene adduct (170) had been established unambiguously by conversion into the bromolactone[56] (171)(Scheme 65). Bromolactonisation was therefore attempted at an

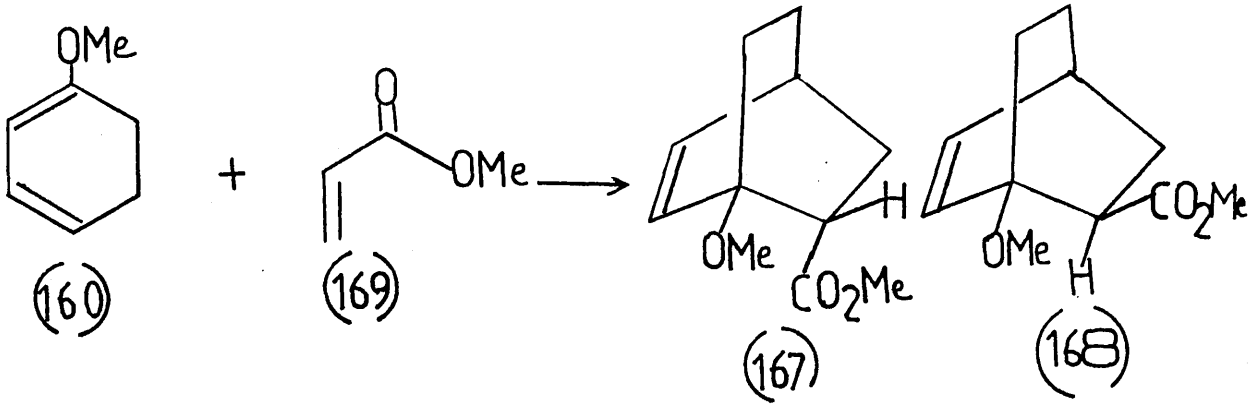


(170) (171)

Scheme 65.

early stage, to establish the stereochemistry of the adducts (161) and (162). Thus, the endo - exo mixture of the acids (163) and (164) was treated with bromine-water in aqueous sodium carbonate under the conditions used successfully for the endo-acid (170). Unexpectedly, the ^1H n.m.r. spectrum of the total reaction product showed no significant signal for a methoxy group. The reaction was repeated with the same result and no identifiable product could be isolated from the reaction mixture.

Birch and Hill[67] reported a closely related reaction, namely addition of methyl acrylate (169) to 1-methoxy-1,3-cyclohexadiene which occurred to give products (Scheme 66), with the ester group (CO_2Me)



Scheme 66.

adjacent to the methoxy group (OMe). That was in accord with other results and theory.[68] In their kinetically controlled reaction, they obtained a mixture of the two isomers (167) and (168) in an endo:exo ratio of 4:1. Base-catalysed equilibration resulted in an increase in the proportion of the exo-isomer (to 40%). This agrees with the equilibrium ratio observed for the corresponding thioaldehyde adducts (161) and (162) and therefore support the foregoing stereochemistry assignment.

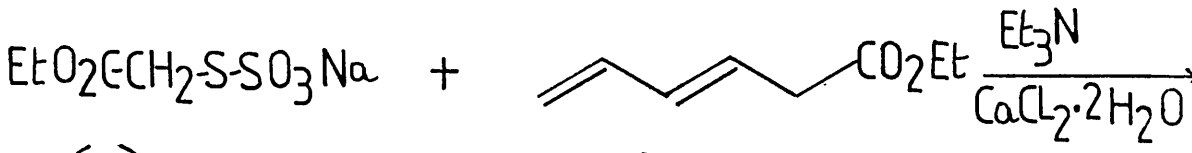
In the hope of producing the other regioisomers, the endo-ester (161) was heated in benzene under reflux for 1h. Unfortunately it remained unchanged. Therefore, the same ester (161) was heated in toluene under reflux. After 1h, a mixture containing the endo (161) and exo-isomers (162) was obtained, but no other compound was produced. in sufficient amount to be identified. This result contrasts with that obtained with the thebaine cycloadduct[56] (142) under the same conditions, when isomerisation to the cycloadduct (143) occurred in high yield. It appears that the 'missing' regioisomers of methoxy-

cyclohexadiene are less stable than that of the corresponding isomer (143) of thebaine.

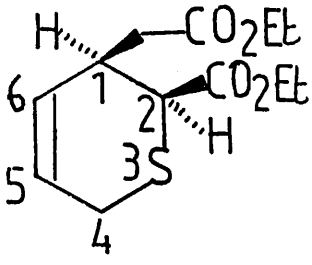
According to molecular orbital calculations on 'simple thioaldehydes', it was concluded[69] that the orientation of unsymmetrical, electron-rich dienes depended upon the atomic coefficient of the LUMO of the thioaldehyde. Strongly electron-withdrawing groups enhance the electrophilic character of the sulphur, i.e. they increase the atomic coefficient, in the thioaldehydes. Therefore, the cycloadducts with the sulphur attached to the more electron-rich (i.e. higher coefficient in the HOMO) end of the dienes are predominantly formed Our results with methoxycyclohexadiene and ethyl thioxoacetate, which has an electron-withdrawing group, agree with these theoretical arguments.

2.2 Cycloaddition of Ethyl Thioxoacetate and 3,5-Hexadienoate.

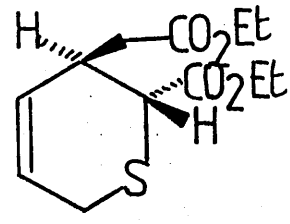
Another example of an unsymmetrical conjugated diene (172) was selected to give an alternative route to a product used by Professor J. K. Sutherland as an intermediate in a thiathromboxane synthesis[70]. Thus, treatment of the Bunte salt (151a) with triethylamine in ethanol-benzene in the presence of 1 mol equivalent of ethyl, 3,5-hexadienoate (172) and calcium chloride dihydrate gave the cycloadducts (173) and (174) in 57% yield after 3 days (Scheme 67). The yield of this reaction was increased to 65% by using 3 mol equivalents of the Bunte salt (151a) for 5 days. The cis:trans ratio was 3:1 as judged from integration of the 2-H signals in the ^{1}H n.m.r. spectrum of the reaction mixture. The two isomers were separated on preparative silica t.l.c. plates and were obtained in approximately the same ratio as determined by integration of the ^{1}H n.m.r. spectrum. The major cis ester gave a signal at 3.45 (J 3.1Hz) for 2-H and the minor trans ester a



(151a) (172)



(173)

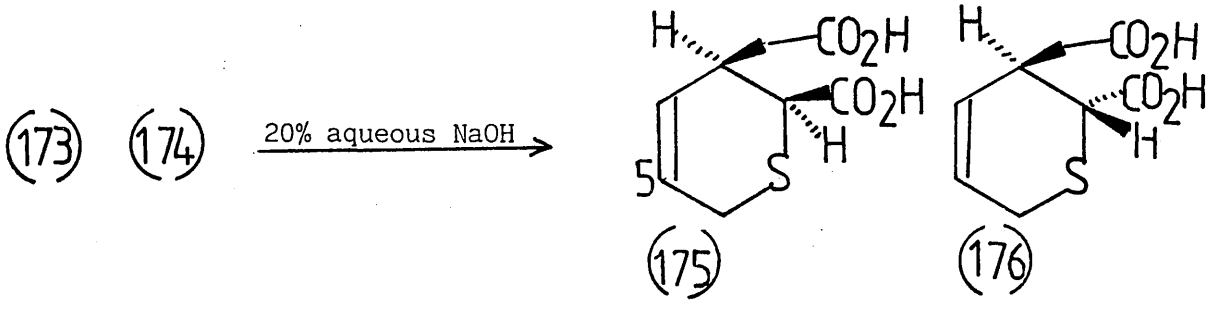


(174)

Scheme 67.

corresponding signal at δ 3.75 (J 4.4Hz).

The molecular formula of the adducts (173) and (174) was determined by accurate mass measurement. The fragmentation patterns are discussed in Chapter 3 (Table 5). The presence of the carbonyl groups was indicated by i.r. spectroscopy, ν_{max} 1730 cm^{-1}. Using the procedure employed by Sutherland, the esters (173) and (174) (3:1) were hydrolysed with 20% aqueous sodium hydroxide in ethanol under reflux (N_2 atmosphere) for 4h (Scheme 68).

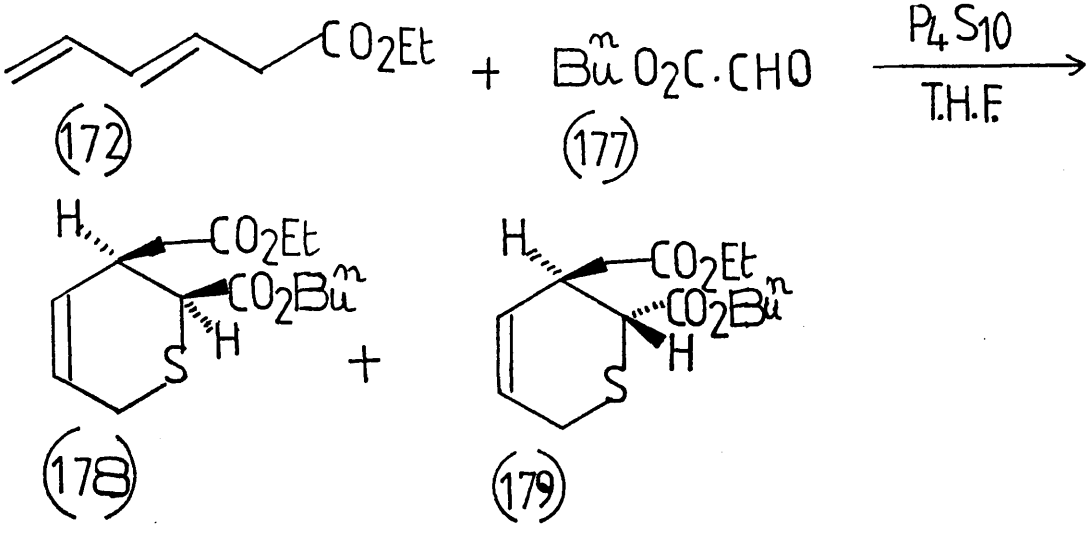


Scheme 68.

The acids (175) and (176) were obtained in 73.5% yield, but in a changed cis:trans ratio of 1:3, as determined by integration of the ^1H n.m.r. spectrum. The mixture of the acids (175) and (176) did not crystallise from any of the usual solvents. The mixture of the esters (173) and (174) (3:1) was again hydrolysed with 20% aqueous sodium hydroxide but, on this occasion, the crystalline trans-diacid (176), m.p. 166-167°C, obtained in 76% yield, was the only detectable product. Microanalysis supported the expected elemental composition, $C_8H_{10}O_4S$. Mass spectroscopy, with accurate mass measurement, confirmed this molecular formula (Chapter 3, Table 6). The i.r. spectrum showed a carboxyl carbonyl band at ν_{max} 1725 cm^{-1}. The ^1H n.m.r. spectra of the esters (173) and (174) and the corresponding acids were closely similar, apart from the replacement of ethoxyl

signals by broad hydroxyl signals and the change of the intensities of 2-H from 3:1 to 1:3, cis:trans in the mixture of acids.

Professor Sutherland very kindly sent us a description of his work. Thus, he treated n-butylglyoxylate (177) with phosphorus pentasulphide (P_4S_{10}) in the presence of ethyl 3,5-hexadienoate (172) in tetrahydrofuran under reflux in a N_2 atmosphere for 20h and obtained a mixture of isomeric cycloadducts (178) and (179) (15%), to which he assigned the stereochemistry cis and trans, in a ratio of 1:3 (Scheme 69). However, when the mixture of the



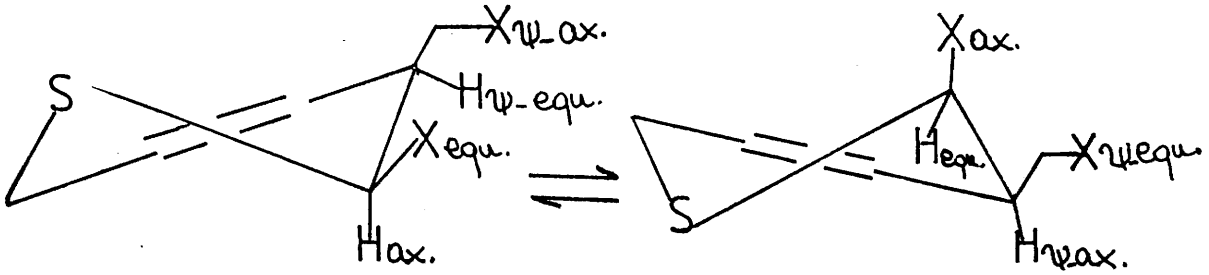
Scheme 69.

esters (178) and (179) (1:3) was hydrolysed with 20% aqueous sodium hydroxide in ethanol under reflux (N_2 atmosphere) for 4h, a good yield of the crystalline acids (175) and (176) was obtained in the same ratio (1:3), m.p. 177-179°C.

The ^1H n.m.r. (CD_3COCD_3, 90MHz) spectra of our acids were essentially in agreement with those of Professor Sutherland. However, we assigned the stereochemistry (173) and (174), the reverse

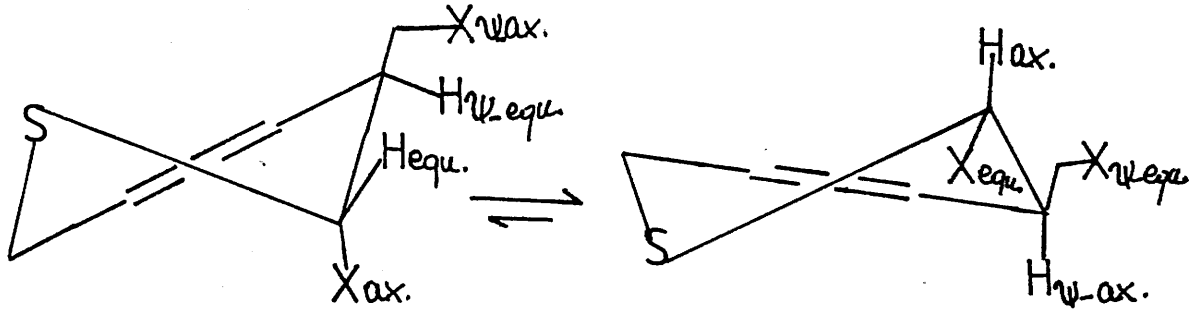
of Professor Sutherland's, for our esters on the basis of the epimerisation observed during hydrolysis with alkali, since the trans-isomer would be expected to be the more stable. Also, formation of the cis-ester as the major product would result from the expected, favourable endo mode of cycloaddition. An attempt was made to effect epimerisation of the mixture of esters (173) and (174) under controlled conditions. However, 0.1M sodium ethoxide at room temperature had no effect and, when the mixture was heated under reflux, a complex mixture of products resulted. The observed coupling constants for 2-H in the cis-isomer (173) (J 3.1Hz) and trans-isomer (174) (J 4.4Hz) are consistent with the assigned stereochemistry, for the following reasons. The four possible half-chair conformers for the cis [(A) and (B)] and trans [(C) and (D)] isomers are drawn in Scheme 70. The two, interconvertible cis-conformers (A) and (B) both have 2-H and 3-H orientated with a dihydral angle of ca. 60°. Thus, according to the Karplus equation, the vicinal coupling constant would have a relatively small value for the cis-isomer, irrespective of the position of the conformational equilibrium, (A) $\rightleftharpoons$ (B). Of the two trans-conformers (C) and (D), the conformer (D) is more stable because the substituents have equatorial and equatorial orientations. Therefore, 2-H in tne trans-isomer would be expected to have a bigger vicinal coupling constant because the 2,3-dihedral angle in the dominant conformation (D) is ca. 180°. This provides a reasonable explanation for the actual values measured for the cis-isomer (J 3.1Hz) and trans (J 4.4Hz).

The regiochemistry of our cycloadduct esters was assigned on the basis of the doublet signals for 2-H in both isomers. The other regio-isomers (180) would be expected to give more complex multiplets, double-doublets or triplets, for the corresponding protons. Furthermore,



(A) (173) (B)

cis

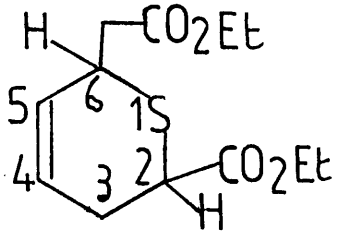


(C) (174) (D)

Trans

$X = CO_2Et$

Scheme 70.

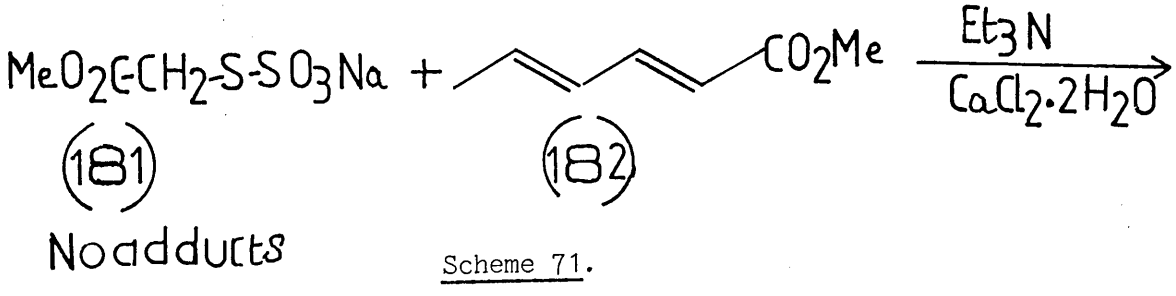


(180)

extensive transformations carried out by Professor Sutherland on his products established their regiochemistry unambiguously.

2.3 Cycloaddition of Methyl Thioxoacetate and Methyl 2,4-Hexadienoate.

A further example of the cycloaddition reaction was attempted. However, treatment of the methyl ester Bunte salt (181) with triethylamine in methanol-benzene in the presence of 1 mol equivalent of methyl 2,4-hexadienoate (182) and calcium chloride dihydrate at room temperature for 4 days gave no cycloadducts (Scheme 71). The ^1H n.m.r. spectrum of the crude product showed signals for methyl sorbate, the disulphide, $(MeO_2C.CH_2S)_2$, and some polymeric material. Since no cycloadduct was obtained, and since we know that the elimination reaction is efficient (perhaps 90%) because, with

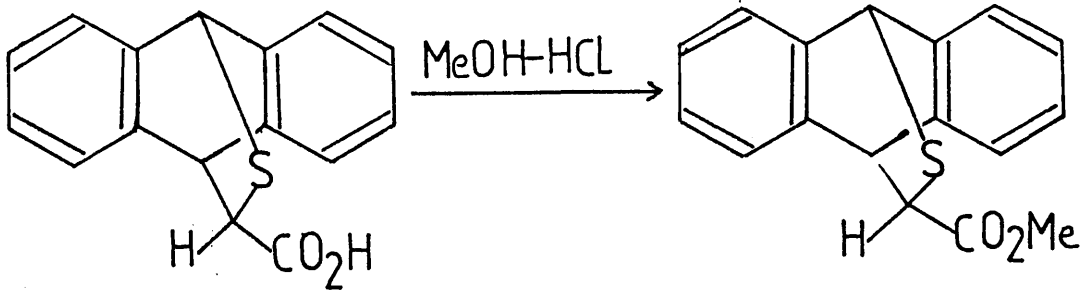


Scheme 71.

the most reactive diene, cyclopentadiene, a high yield of cycloadduct was obtained[60], it seemed likely that the cycloaddition of the thio-

aldehyde was slow. Thus, trapping by the diene could not compete effectively with other reactions such as polymerisation and reaction with the strongly nucleophilic sulphite (SO_3^{2-}). It appears therefore that the thioaldehyde reacts only slowly with the diene (182) having an electron-withdrawing ester group.

When the methyl ester Bunte salt (181) and methyl sorbate (182) did not yield any cycloadduct under the usual conditions, an alternative source of the thioaldehyde was investigated. Thus, treatment of anthracene cycloadduct acid (183) with dry methanolic hydrogen chloride (prepared from methanol and acetyl chloride) gave the desired crystalline ester (184) in 95% yield (Scheme 72), m.p. 147-148°C. Microanalysis supported the expected elemental composition, $C_{17}H_{14}O_2S$. Mass spectrometry, with mass measurement, confirmed this molecular formula. The i.r. spectrum showed a carbonyl band



(183) (184)

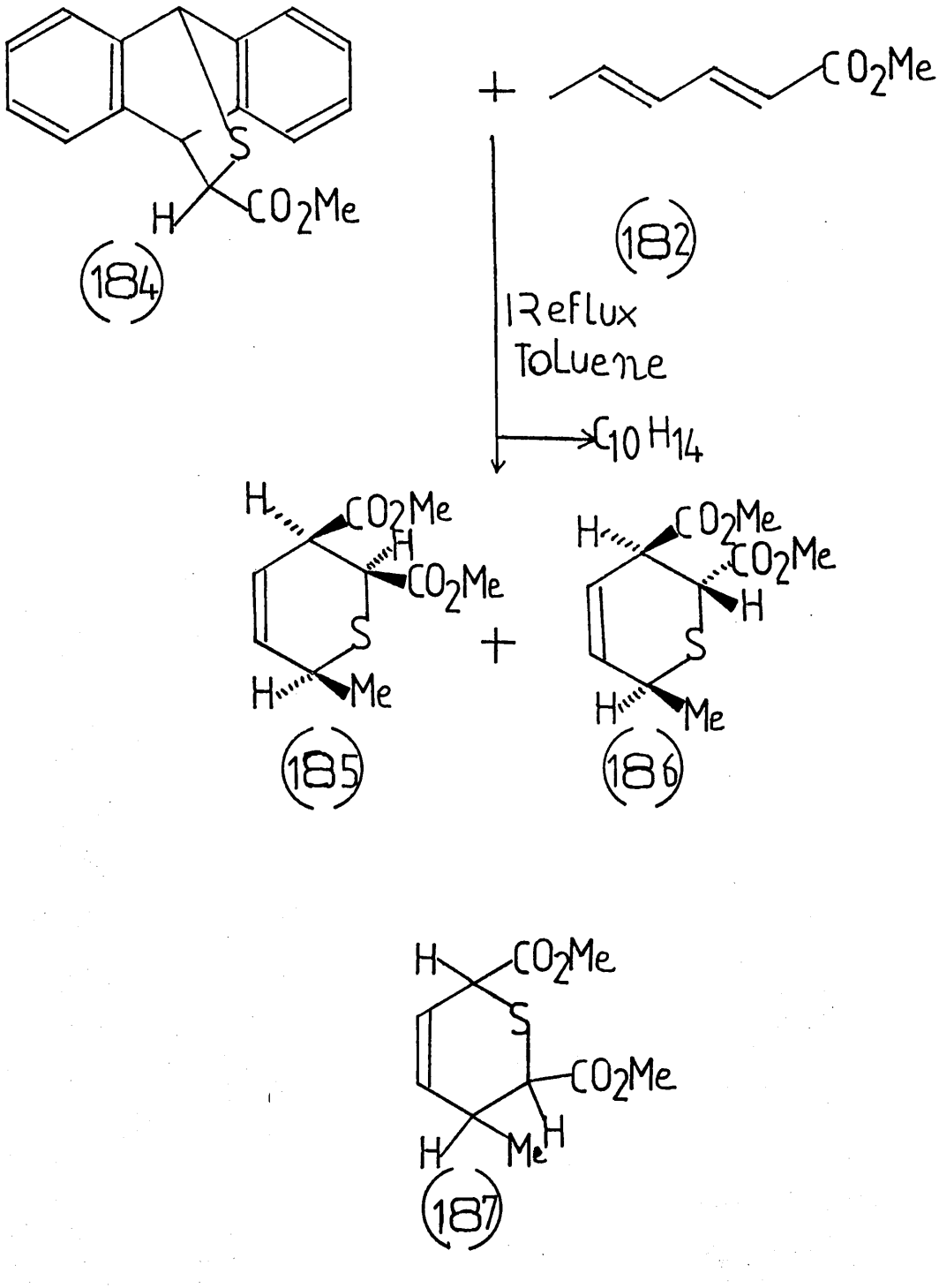
Scheme 72.

at ν_{max} 1740 cm^{-1}. The ^1H n.m.r. spectra of the ester (184) and the corresponding acid (183) were closely similar, apart from the replacement of the broad hydroxyl signal by the methoxyl signal. The cycloadducts (185) and (186) were obtained using the alternative

method for generating methyl thioxoacetate, that is by thermal dissociation of the anthracene cycloadduct (184). Thus, the anthracene adduct (184) was heated under reflux in toluene with methyl sorbate (1 mol equivalent) overnight, by which time all the anthracene adduct (184) had decomposed (Scheme 73). The ^{1}H n.m.r. spectrum of the reaction mixture showed the formation of cycloadducts (185) and (186) in a cis:trans ratio of 3:2 as judged from integration of the 2-H signals. The crude mixture was chromatographed on a silica column and gave the adducts (185) and (186) in a 81% yield. The two isomers were separated on preparative silica t.l.c. plates and were obtained in approximately the same ratio as determined by integration of the ^{1}H n.m.r. spectrum. The major, cis-cis ester gave a signal at δ 4.11(J. 5.0Hz) for 2-H and the minor, trans ester a corresponding signal at δ 3.95 (J 4.0Hz). The molecular formula of the cycloadducts (185) and (186) was determined by accurate mass measurement (see Chapter 3, Table 7). The presence of the carbonyl groups was indicated by i.r. bands at ν_{max} 1735 cm^{-1}.

The regiochemistry of the cycloadduct esters (185) and (186) was assigned on the basis of the chemical shifts of the methine protons (3-H), δ 3.60 (185) and 3.64 (186). In contrast, in the other possible regio-isomers (187), of either stereochemistry the corresponding proton (6-H) is adjacent to both a double bond and sulphur. Therefore, the signal for this proton would be shifted further downfield relatively to that for 2-H [δ 4.11 in (185) and 3.95 in (186)].

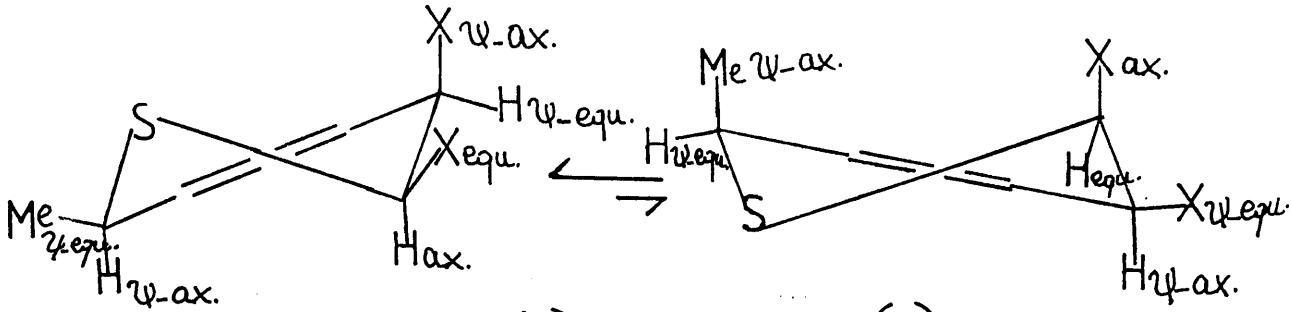
Conformations for the cycloadducts (185) [(A) and (B)] and (186) [(C) and (D)] are drawn in Scheme 74. It is assumed that the 6-methyl and 3- ester groups will be cis since the trans-trans diene (182) was used in the Diels-Alder reaction. Again, one would expect


S
H
CO2Me
(184)
+
CO2Me
(182)
Reflux
Toluene
C10H14
H
CO2Me
H
CO2Me
S
H
Me
(185)
+
H
CO2Me
CO2Me
H
S
H
Me
(186)
H
CO2Me
S
CO2Me
H
Me
H
(187)

Scheme 73.

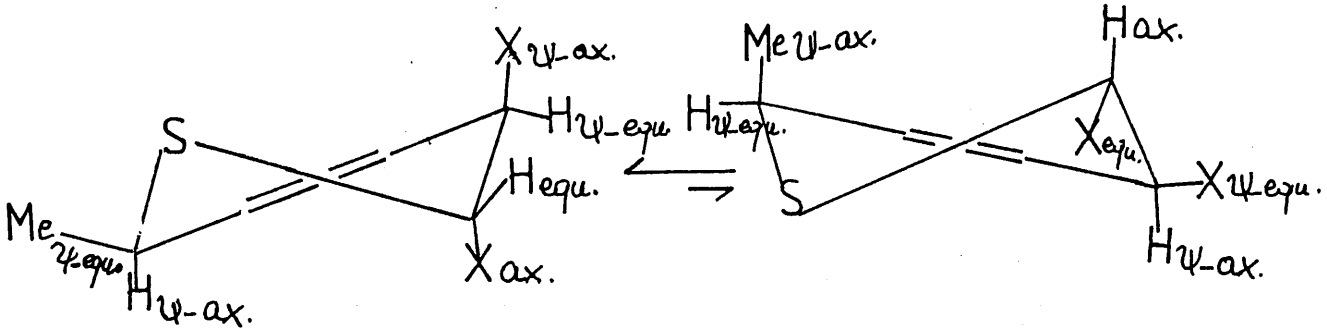
that endo addition of the thioaldehyde would be favoured, leading to the 3,6-cis-2,3-cis isomer (185) as the major product. However the 2,3-coupling constant for the major product (185) (J 5.0Hz) was greater than that (J 4.0Hz) for the minor product (186). The reverse was true for the isomeric cycloadducts (J 3.1Hz) and (J 4.4Hz) (Scheme 70) formed from ethyl 3,5-hexadienoate. The reason for this change in relative size of vicinal coupling constants is not clear, although the conformational equilibria for the 2 pairs of products will certainly be different. Thus, for the cis-cis isomer (185), conformation (A) having a ψ-equatorial methyl group will be favoured over (B). Further, for the cis-trans isomer (186), conformation (D), having a ψ-axial methyl group, will be less strongly favoured over (C) than was the case (Scheme 70) for the trans cycloadduct (174). However, it is not possible to predict the outcome confidently without knowing the position of the equilibria and, importantly, the dihedral angles between vicinal, i.e. equatorial-ψ-equatorial, axial-ψ-equatorial, and equatorial-ψ-axial, bonds. It was hoped that base-catalysed epimerisation of the esters (185) and (186) might provide evidence for the stereochemistry, as it did for the other pair of cycloadducts (173) and (174), described before. Unfortunately, migration of the double bond occurred under the vigorous conditions employed as follows.

The esters (185) and (186) were hydrolysed with 20% aqueous sodium hydroxide in methanol under reflux (N_2 atmosphere) for 4h. The diacid (187) was obtained in 85% yield (Scheme 75). The ^1H n.m.r spectrum of the crude mixture showed no olefinic proton signals. This could be explained by migration of the double bond to the 2,3-position in the compound (187), as a consequence of the acidity of the proton at position 3. The diacid (187) was subjected to Kugelrohr distillation. The major part of the material distilled



(A) (185) (B)

cis-cis



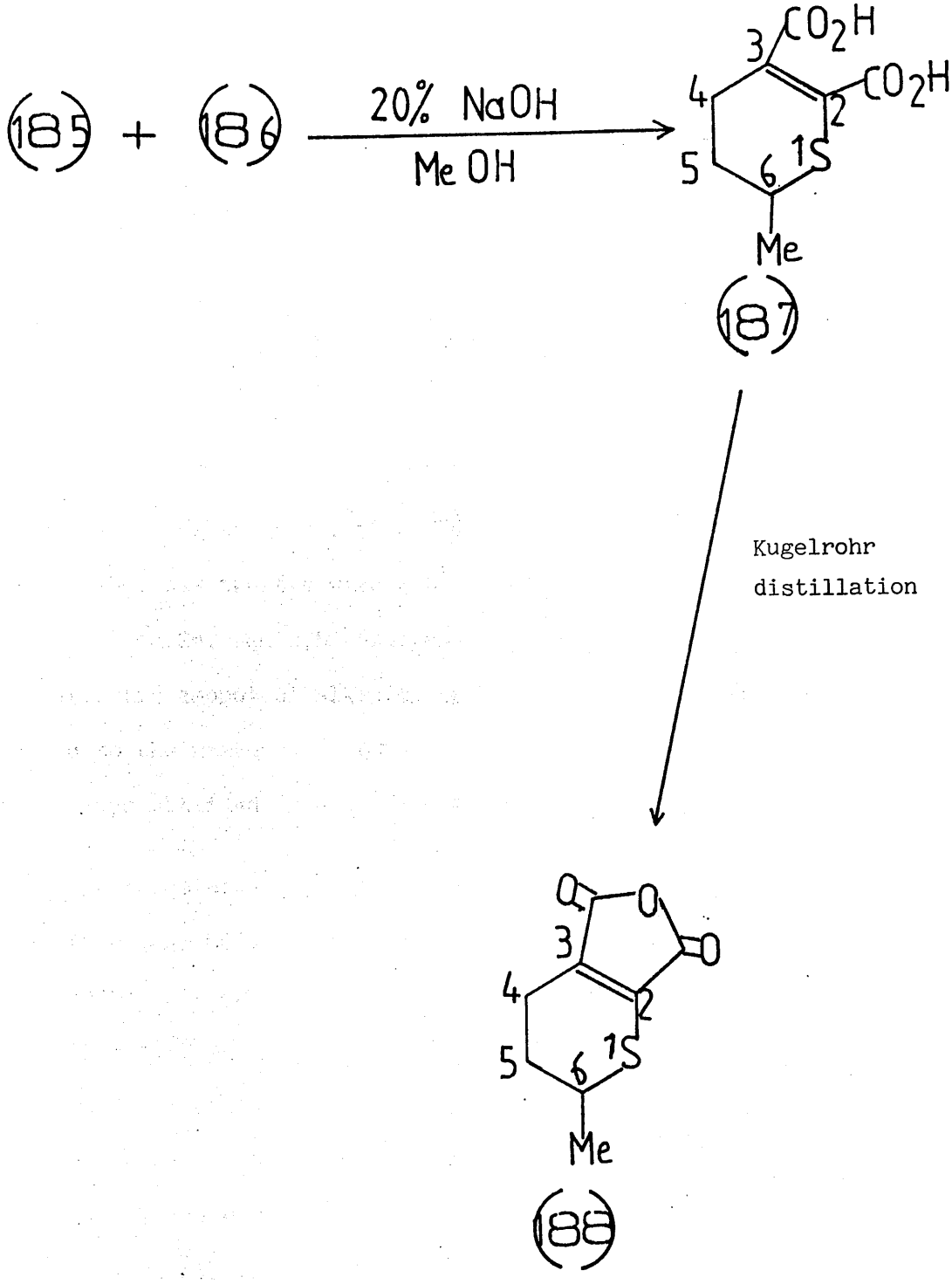
(C) (186) (D)

cis-trans

X = CO_2Me

Scheme 74.

to give anhydride (188) as a yellow oil (Scheme 75). The molecular



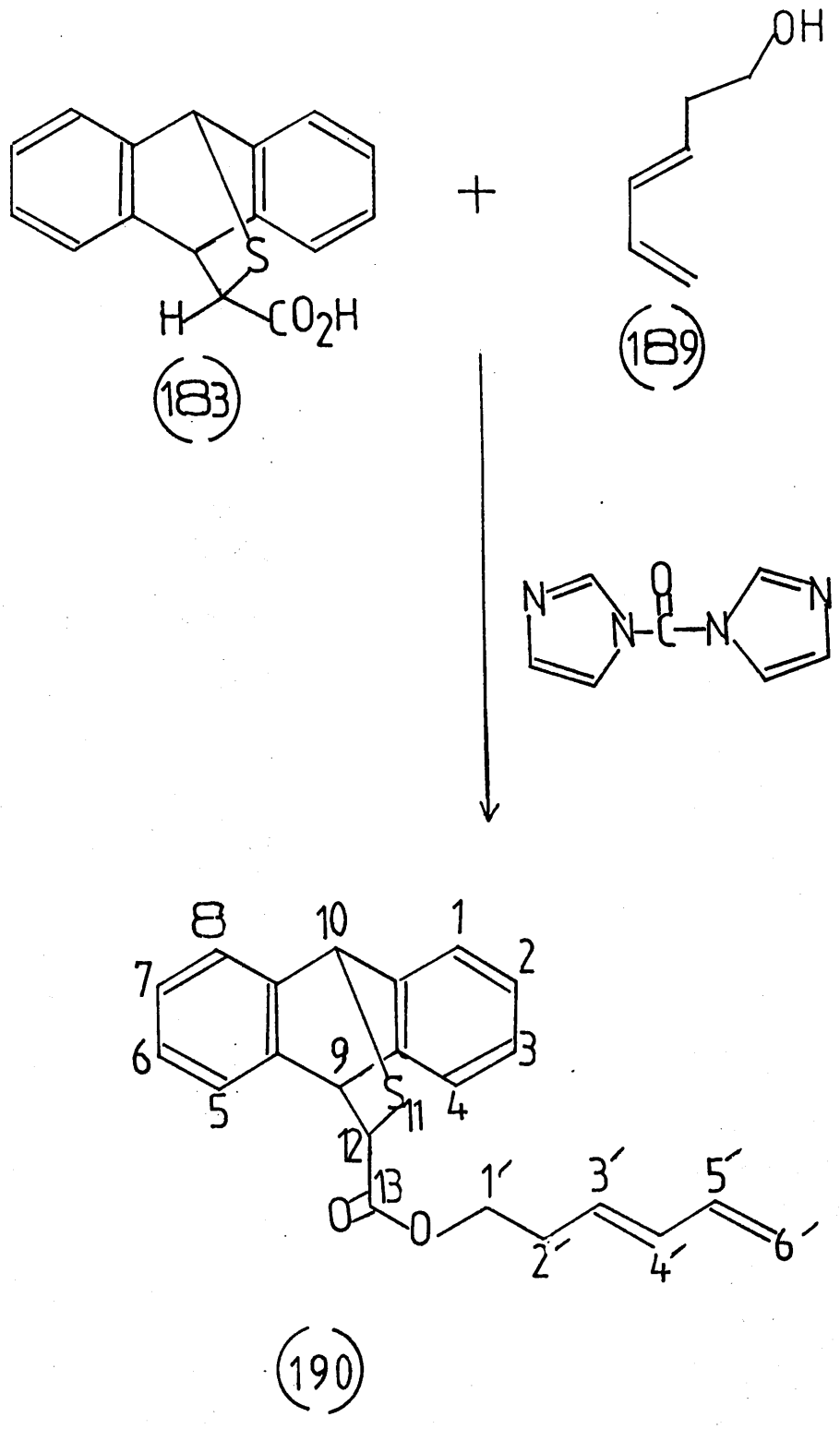
Scheme 75.

formula of the anhydride (188) was determined by accurate mass measurement. The fragmentation pattern also supported the structure (188) (see Chapter 3, Table 8). The presence of the anhydride group was indicated by i.r. spectroscopy, ν_{max} 1850 (weak bond) and 1775 cm^{-1}. These were in agreement with the reported[71] values of the carbonyl groups in maleic anhydride, ν_{max} 1850 (weak bond) and 1790 cm^{-1} (strong bond).

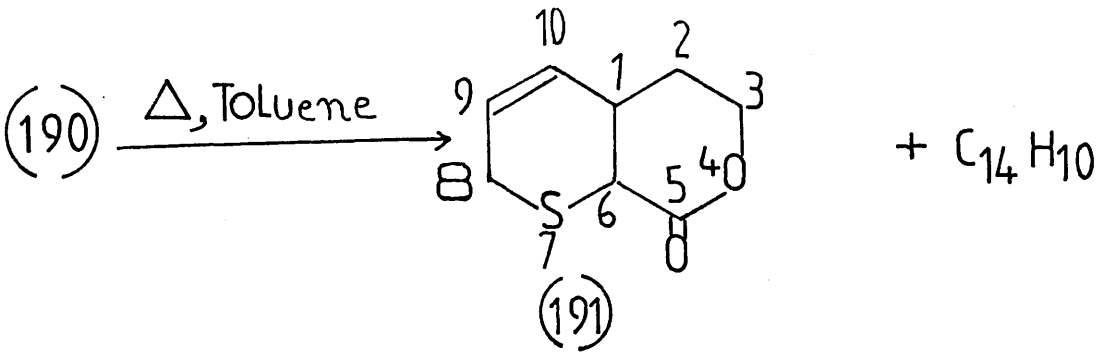
2.4 Intramolecular Diels-Alder Reaction of 3,5-Hexadienyl Thioxoacetate.

Following the report by Baldwin and Lopez[51] of an intramolecular Diels-Alder trapping of an aliphatic thioaldehyde, we decided to attempt a similar reaction. To this end, the anthracene cycloadduct-acid (183) was treated with N,N′-carbonyldi-imidazole in dichloromethane for 2h, and 3,5-hexadien-1-ol (189) (1 mol equiv.), containing a catalytic amount of alkoxide (generated with n-butyl-lithium), was added to the mixture. After 24h, the anthracene cycloadduct ester (190) was obtained in 44% yield after chromatography Scheme 76.

The molecular formula of the adduct (190) was determined by accurate mass measurement (see Chapter 3, Table 9). The presence of the carbonyl group was indicated by i.r. spectroscopy, ν_{max} 1735 cm^{-1}. The ^1H n.m.r. was essentially similar to the combined spectra of the starting materials, apart from the absence of the hydroxyl signals. The hexadienyl ester (190) of the anthracene cycloadduct was heated in toluene under reflux for 4h to afford a crude mixture which gave a ^1H n.m.r. spectrum showing signals for the expected lactone (191) (Scheme 77).



Scheme 76.



Scheme 77.

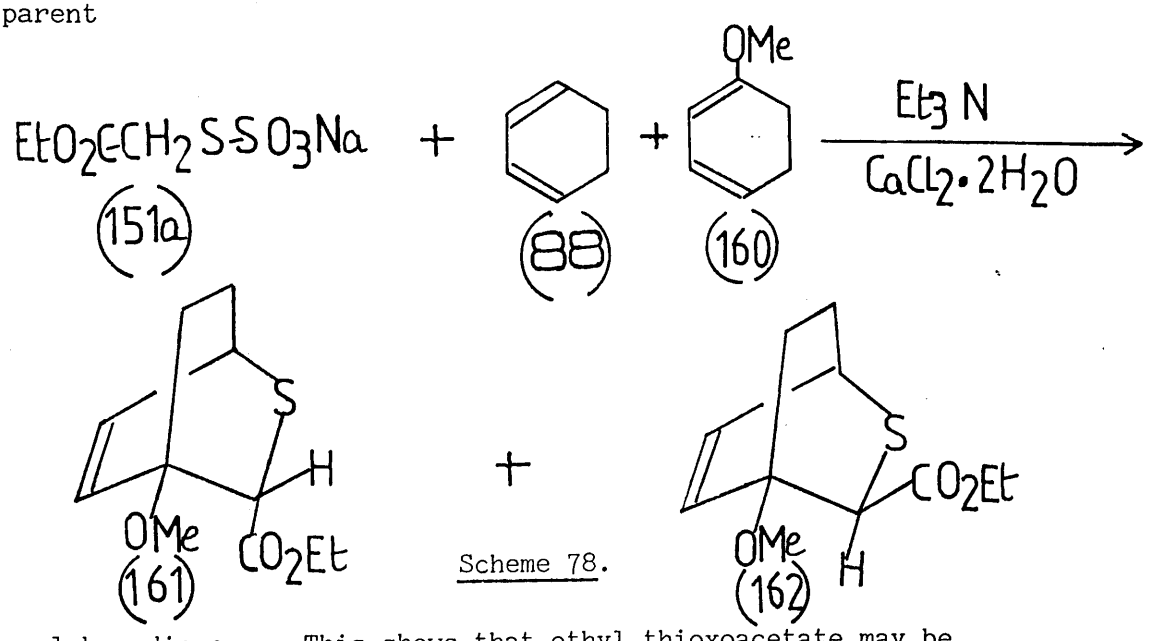
The mixture was chromatographed on a silica short column, then the lactone (191) was isolated on preparative t.l.c. plates as a gum in 46% yield.

The molecular formula of the product (191) was determined by accurate mass measurement (see Chapter 3, Table 10). The presence of the carbonyl group was indicated by i.r. spectroscopy, ν_{max} 1735 cm^{-1}. The ^1H n.m.r. spectrum showed three multiplets at δ 1.7-2.2, 3.0 and 3.15 for 2-CH_2, 1-H and 8-CH_2, respectively. The 3-CH_2 group, attached to oxygen, gave a triplet further downfield at δ 4.35 as expected. The proton 6-H gave a doublet at 3.77 with a coupling constant of 5.8Hz suggesting a cis ring fusion. The olefinic protons 9-H and 10-H resonated in the usual region, δ 5.70 and 6.01 (m, 10- and 9-H).

2.5 Competition Reactions.

It is not possible to measure directly the rates of cycloaddition of transient intermediates like thioaldehydes with various dienes. However, it is possible to compare relative rates by measuring the yields of cycloadducts formed competively from mixtures of pairs of conjugated dienes. Thus, treatment of 1-methoxy-1,3-cyclohexadiene and 1,3-cyclohexadiene in equimolecular amounts with 1 molecular equivalent

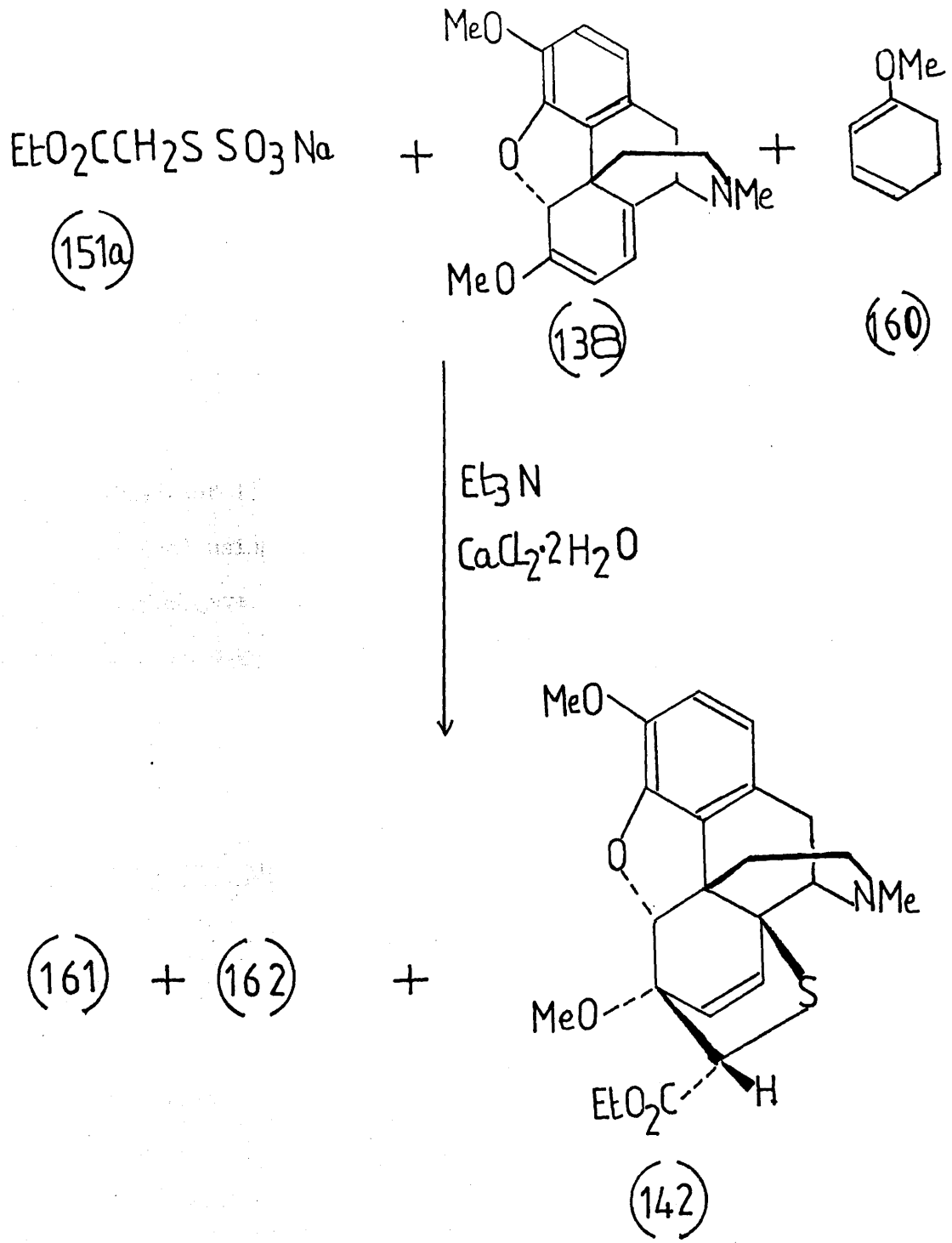
of the Bunte salt (151a) under the usual conditions gave the cycloadducts (161) and (162) of methoxycyclohexadiene in 65% yield in an endo:exo ratio of 4:1 (Scheme 78). This composition was determined from the ^{1}H n.m.r. spectrum of the reaction mixture, which was essentially similar to that of the methoxy cyclohexadiene cycloadducts. No significant amounts of the cycloadducts of cyclohexadiene were formed even when the experiments was repeated using 2 mol equivalents of this diene. This conclusion was based on the absence of signals for the cycloadduct (140) of cyclohexadiene in the region δ 6.29 and δ 6.69. It is clear therefore that the methoxydiene is much more reactive towards the thioaldehyde than the parent



Scheme 78.

cyclohexadiene. This shows that ethyl thioxoacetate may be classified as an electrophilic or electron-demanding dienophile.

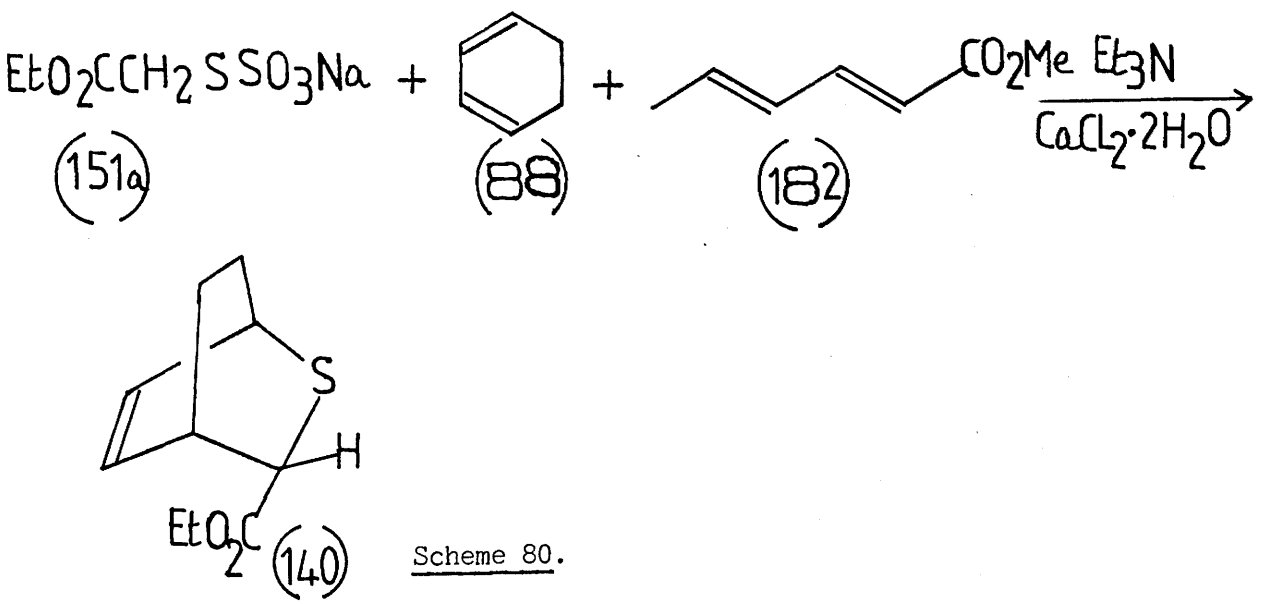
As expected, there was a much smaller difference in the relative reactivities of methoxycyclohexadiene and thebaine (138). Treatment of 1-methoxy-1,3-cyclohexadiene and thebaine with the Bunte salt (151a) using 1 mol equivalent of each, gave the corresponding cycloadducts in approximately equal amounts after 5 days (Scheme 79). The ^{1}H n.m.r. spectrum of each isomer of the methoxydiene adduct was identical with that observed before and also the spectrum of the


EtO2CCH2S SO3Na
(151a)
MeO
O
NMe
MeO
(138)
OMe
(160)
Et3N
CaCl2·2H2O
(161) + (162) +
MeO
O
NMe
S
MeO
EtO2C
H
(142)

Scheme 79.

thebaine adduct (142) agreed completely with that reported[56] in the literature. It is interesting that the sterically crowded methoxy-cyclohexadiene ring of thebaine is as reactive as that of the parent compound, especially since thebaine is attached essentially exclusively from only one (β) face. It is possible that strain imposed by the 4,5-oxide bridge in thebaine increases the reactivity of the diene system.

Treatment of 1,3-cyclohexadiene and methyl sorbate with the Bunte salt (151a) using 1 mol equivalent of each reactant under the usual conditions gave the cycloadduct (140) of 1,3-cyclohexadiene in good yield. No significant amounts of the adducts of methyl sorbate were formed Scheme 80. The ^{1}H.n.m.r. spectrum of the reaction

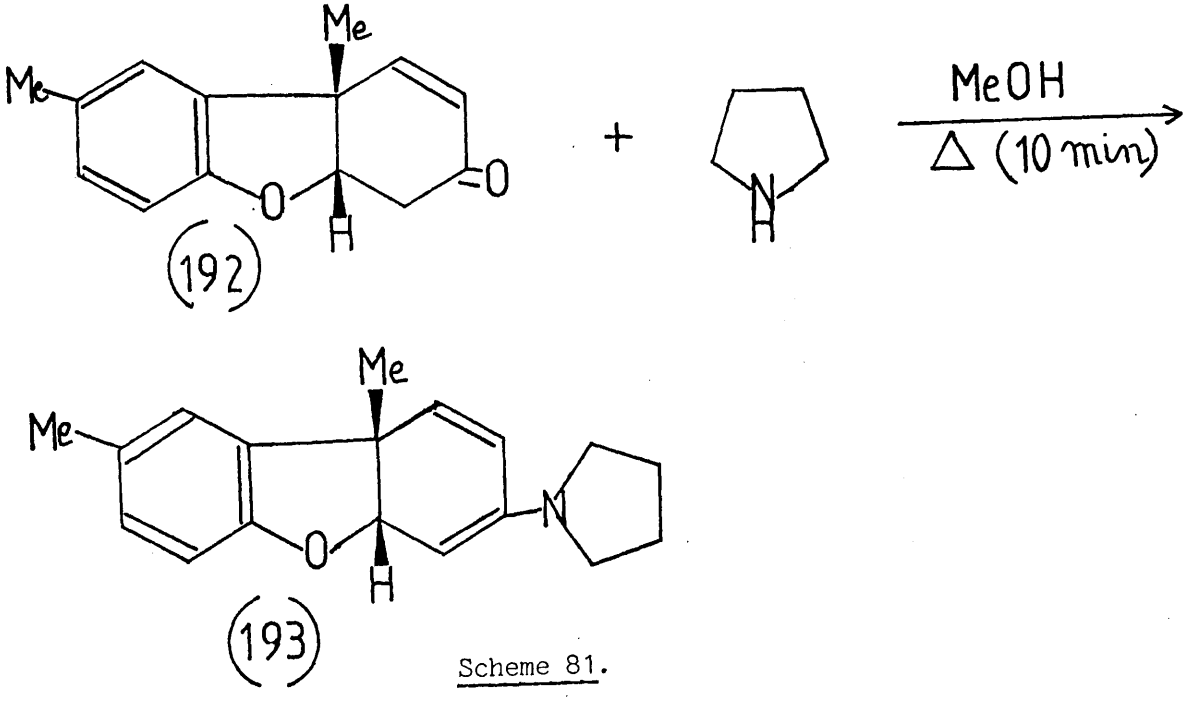


Scheme 80.

mixture showed only signals attributable to the 1,3-cyclohexadiene adduct (140). This result confirms the earlier conclusion, based on failure to obtain the methyl sorbate cycloadducts directly using the Bunte salt, that the diene is deactivated towards electron-demanding dienophiles by the ester group.

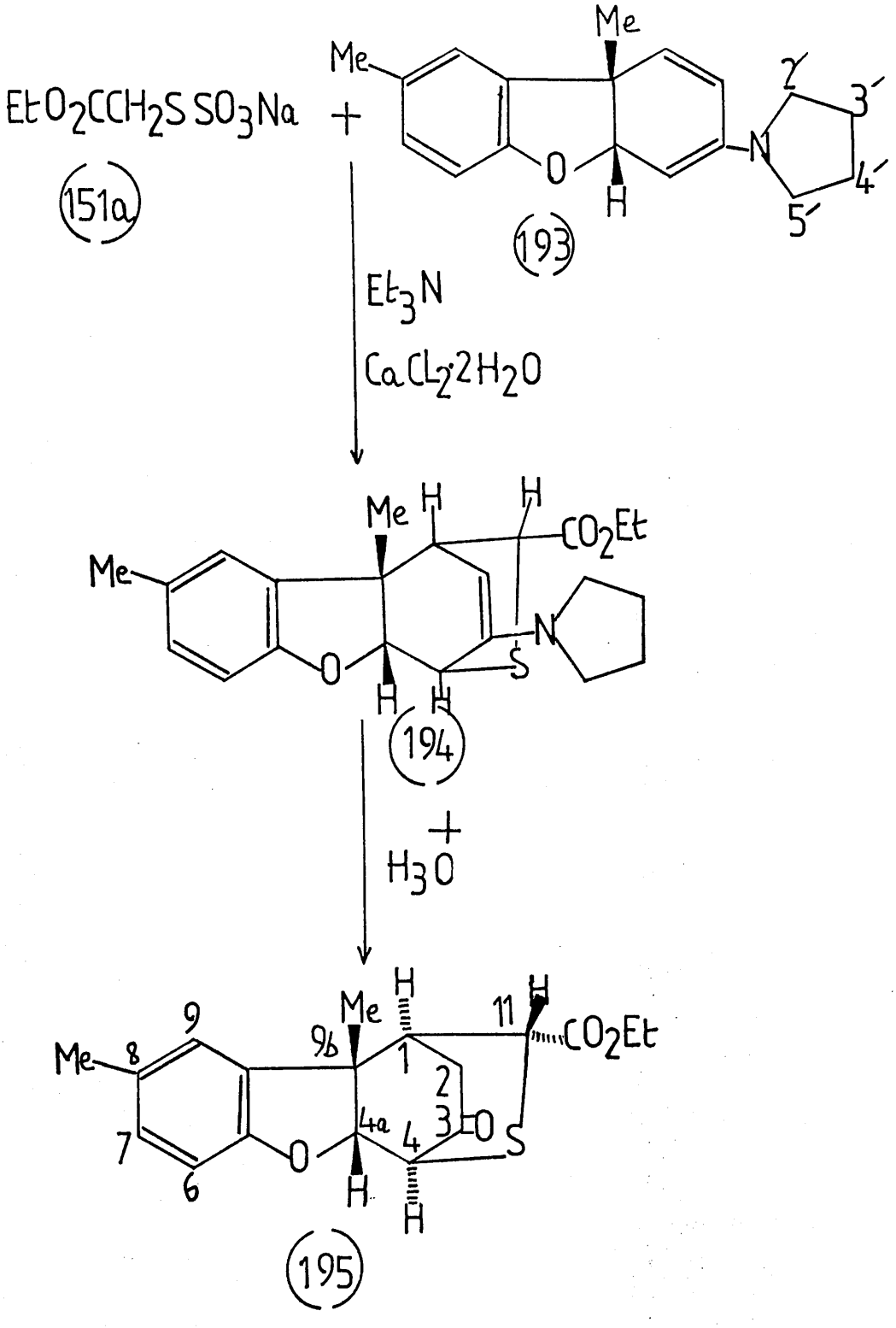
2.6 Cycloaddition Reaction of Ethyl Thioxoacetate and the Dienamine Derived from Pummerer's Ketone.

With the aim of extending the study of thioxoacetate ester reactions with unsymmetrical conjugated dienes, a diene substituted in the 2-H position with an amino group was selected. The compound chosen was the dienamine (193) prepared[72] from the readily accessible enone, Pummerer's ketone (192) (Scheme 81). The dienamine was formed as



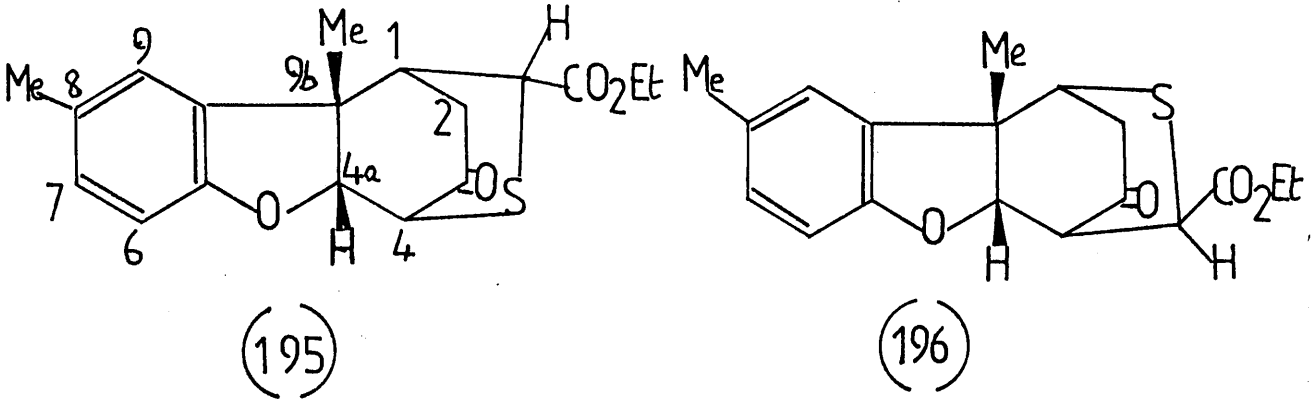
Scheme 81.

an oil, from the ketone and pyrrolidine in methanol, as described[72], and used immediately without purification. The Bunte salt (151a) was treated with triethylamine in ethanol-benzene in the presence of 1 mol equivalent of the dienamine (193) and calcium chloride dihydrate in the usual way for 3 days. The mixture was worked-up under acidic conditions, which presumably hydrolysed the enamine (194), to give the cycloadduct (195) as a gum in 18% yield (Scheme 82). The yield of this product was increased to 33% by using 3 mol equivalents of the Bunte salt (151a) for 4 days. Purification of the adduct (195) was carried out on preparative silica t.l.c. plates.


EtO2CCH2S SO3Na
(151a)
+
Me
Me
O
H
N
2'
3'
4'
5'
(193)
Et3N
CaCl2·2H2O
Me
H
H
CO2Et
Me
O
N
S
H
H
(194)
+
H3O
H
Me
H
11
CO2Et
9
8
9b
1
2
3
4a
4
O
S
7
6
O
H
H
(195)

Scheme 82.

The molecular formula of the cycloadduct (195) was determined by accurate mass measurement. The fragmentation patterns are discussed in Chapter 3 (Table 11). The presence of the carbonyl groups was confirmed by i.r. spectroscopy; a strong band at ν_{max} 1730 cm^{-1} was attributed to both carbonyl groups. The structure of the adduct (195), with the exception of stereochemistry, was assigned on the basis of the ^1H n.m.r. spectrum. The 90 MHz spectrum distinguishes between the 2 possible regioisomers (195) and (196) (Scheme 83). The 4a-H signal, δ 4.86 (d,J 4.0Hz), is easily

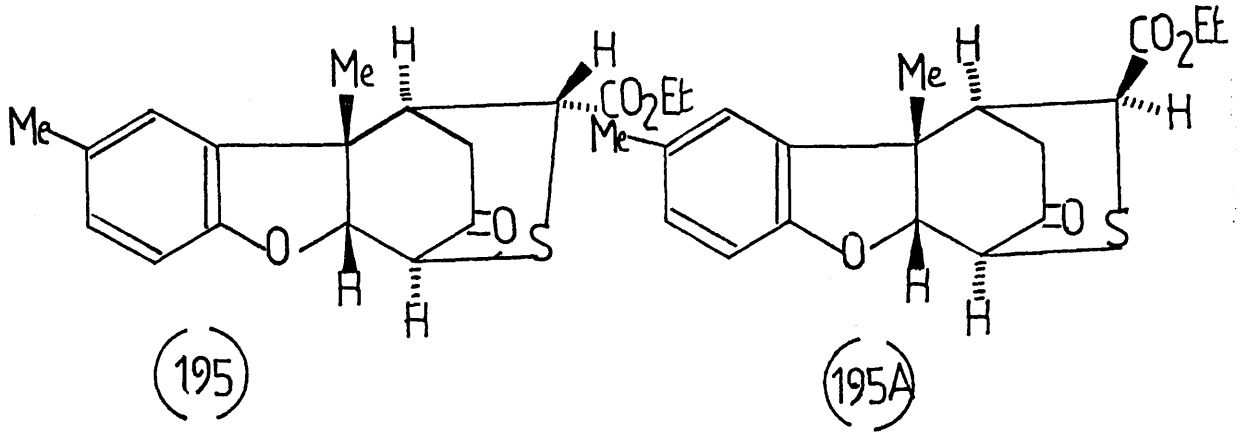


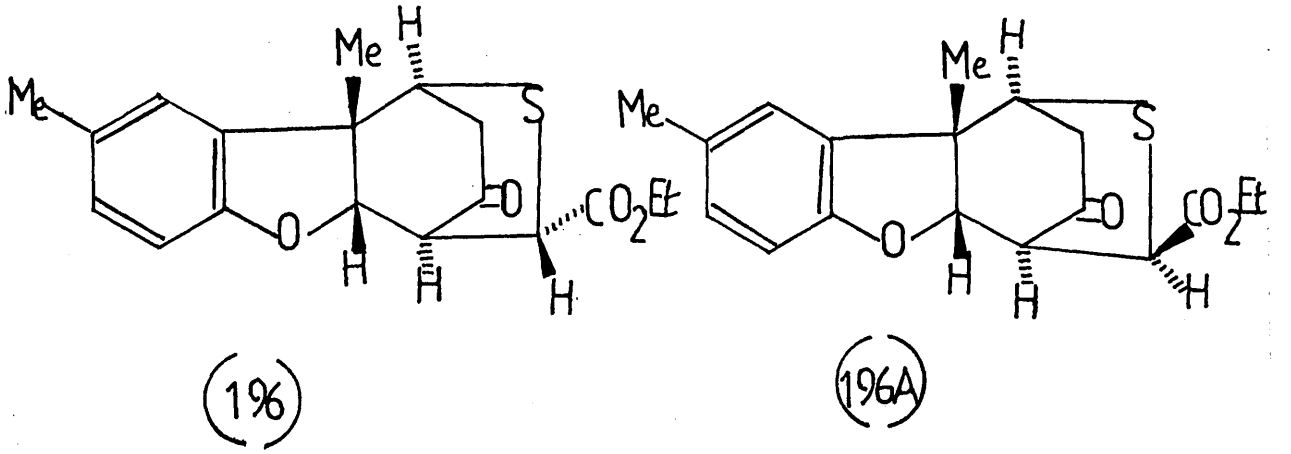
Scheme 83.

recognised by its low field position, similar to that of the corresponding signal, δ 4.65, in Pummerer's ketone (192), arising from deshielding by the inductive effect of oxygen. This allows identification of the signal for 4-H, δ 3.35 (d,J 4Hz), since no other signals have this splitting. The fact that this signal is a clean doublet discounts structure (196), since 4-H would be coupled with 11-H.

It was not possible to determine the stereochemistry (i.e. which of 4, racemic, diastereoisomers (195) is, assuming that the cis ring fusion of Pummerer's ketone is maintained) from the 90 MHz spectrum

(Scheme 84). However, the 200 MHz spectrum and n.Oe studied (Tables 1 and 2) established the structure (195) unambiguously. The structure (195) can be distinguished from (195A) by the long-range 'W' coupling, J 1.3Hz, between 11-H and 2α-H. This coupling would not be expected in the isomer (195A).

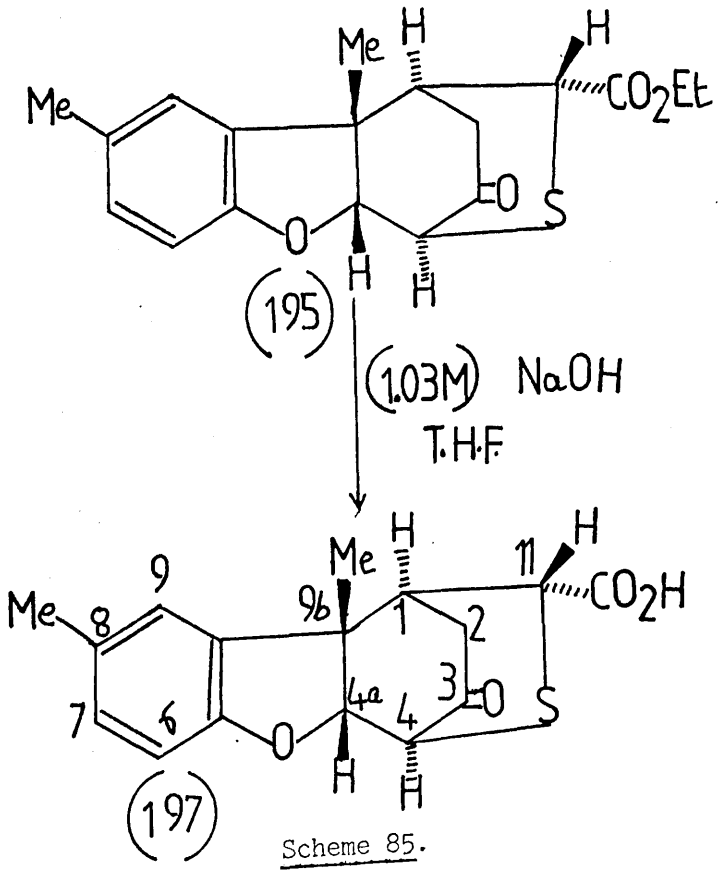




Scheme 84

Importantly, this is supported by n.O.e experiments. Thus, irradiation at δ 4.11 (11-H) increased the intensity of the singlet centered at δ 1.63 (9b-Me). Conversely, the doublet at δ 4.11 (11-H) increased in intensity when the methyl group, δ 1.63, was irradiated. These observations establish the relative stereochemistry at the centres 11, 1, and 9b, and also confirm the regiochemistry.

When the cycloadduct (195) was hydrolysed with 1.03M sodium hydroxide in tetrahydrofuran at room temperature the acid (197) was obtained as a gum in 83% yield (Scheme 85). The molecular formula, $C_{16}H_{16}O_4S$, was determined by accurate mass measurement (see Chapter 3, Table 12). The i.r. spectrum showed a broad, strong band at ν_{max} 1730 cm^{-1}, arising from the ketonic and carboxylic carbonyl groups. The ^1H n.m.r. spectra of the ester (195) and the acid (197) were closely similar, apart from the replacement of ethoxyl signals by broad hydroxyl signal, which disappeared upon exchange with deuterium



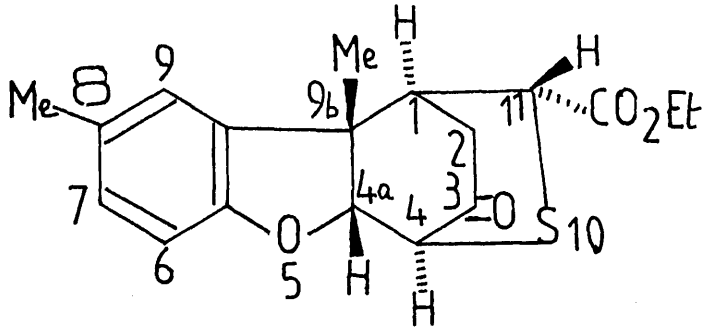
Scheme 85.

oxide.

It was hoped that a crystalline product, suitable for combustion analysis, would be obtained. However, so far the acid (197) has resisted crystallisation.

The formation of predominantly only one (195) of eight possible diastereoisomers requires comment. Vedejs et al reported[48] a related cycloaddition reaction. They found that the thioaldehydes having electron-withdrawing groups (ZCHS;Z=CN,CO_2CH_3, or $COCH_3$), generated from the phenacyl sulphides (93), could be trapped by 2-ethoxybutadiene to give Diels-Alder adducts (see Chapter 1, Scheme 39). The compounds with sulphur attached to C(1) of the diene were found to be formed predominantly. This regiochemistry corresponds to that observed in the reaction of thioxoacetate (137a) and the dienamine (193). The unusually high endo selectivity of the latter reaction could be due to the strong steric repulsion between the 9b-methyl and ester groups in the exo isomer. Finally, attack by the thioaldehyde on the dienamine (194) has occurred cis to the 9b-methyl group and 4a-hydrogen atom and trans to the larger 9b-aryl group and 4a-oxygen atom. The 200 MHz ^1H n.m.r spectrum showed weak signals that could represent another isomer but otherwise the reaction was remarkably stereo- and regio- selective.

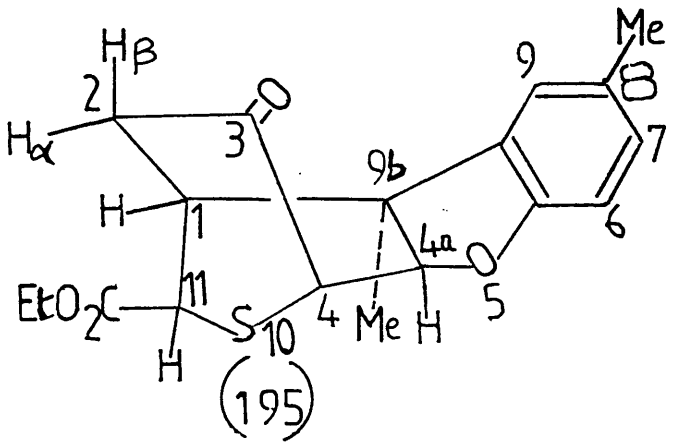
Table 1. 200 MHz ^{1}H n.m.r. spectrum of the cycloadduct (195)



(195)

Protons	δ p.p.m.	Coupling constants (Hz)
7	6.93	ddq, J 8.2, 1.9 and 0.6
9	6.86	dp, J 1.9 and 0.6
6	6.61	dm, J 8.2 and <0.4
4a	4.86	dd, J 4.0 and 0.7
OCH_2CH_3	4.21	q, J 7.2
11	4.11	dd, J 2.9 and 1.3
4	3.35	d, J 4.0
1	2.92	qd, J 3.1 and 0.8
2β	2.57	dd, J 19.8 and 3.1
8-Me	2.26	s, with fine splitting
2α	1.97	ddd, J 19.8, 3.3 and 1.3
9b-CH_3	1.63	s
OCH_2CH_3	1.28	t, J 7.2

Table 2. Nuclear Overhauser difference spectra ($CDCl_3$; 200 MHz) n.O.e.



Protons irradiated	δ	1-H	2β-H	2α-H	4-H	4a-H	6-H	7-H	8-Me	9-H	9b-Me	11-H	OCH_2CH_3	OCH_2CH_3
1-H	2.92	-74.75	2.06	1.62	0.09	0.17	0.14	0.53	0.03	4.54	1.47	4.78	0.64	0.45
2β-H	2.57	2.72	-56.59	21.16	0.26	0.26	0.32	0.23	0.31	0.67	-0.3	-0.03	0.24	0.13
2α-H	1.97	1.99	20.95	-62.44	0.26	-0.01	0.16	0.09	-0.71	-0.13	-0.15	0.29	0.51	0.29
4-H	3.35	-0.03	0.08	0.26	-65.22	6.1	0.08	0.07	0.07	0.08	-0.12	-0.06	0.17	0.12
4a-H	4.86	0.08	0.12	0.22	7.98	-83.16	0.2	0.12	0.36	0.06	2.71	0.06	0.56	0.09
8-Me	2.26	0.01	0.09	-0,52	0.09	0.38	0.21	7.02	-262.8	6.98	0.1	0.06	0.16	0.32
9b-Me	1.63	4.37	0.34	0.59	-0.43	11.28	0.57	0.31	0.8	4.68	-224.96	18.83	0.96	0.40
11-H	4.11	5.62	-0,24	0.30	0.36	0.91	0.07	-0.27	0.19	0.14	6.73	-76.67	-7.37	0.52
OCH_2CH_3	4.21	0.40	0.17	0.35	0.13	0.26	0.09	0.22	0.30	0.05	0.57	-6.58	-150.13	4.98
OCH_2CH_3	1.28	0.13	0.07	0.27	0.09	0.12	0.12	0.30	0.26	0.13	0.04	0.28	4.56	-232.28

CHAPTER THREE

MASS SPECTRA OF THE NEW COMPOUNDS

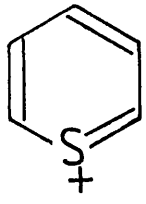
Mass Spectra of Thioaldehyde Cycloadducts and their Derivatives.

High resolution mass spectra (electron impact, 70 ev) were measured for the new cycloadducts, and certain derivatives, to confirm the molecular formulae and provide supporting evidence for the structures. The most significant peaks are listed in Tables 3-13, together with possible interpretations of the constitution of fragment ions. A few features of special interest are discussed briefly, as follows.

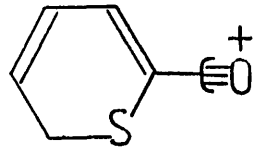
Retro-Diels-Alder Cleavage. The bridged cycloadducts (161) and (162), and the corresponding acids (163) and (164), of methoxycyclohexadiene gave base peaks, $C_7H_{12}O^{+\bullet}$, arising presumably, from retro-Diels-Alder fragmentation (Tables 3 and 4). Similarly, the anthracene adducts (184) and (190) gave intense peaks, $C_{14}H_{10}^{+\bullet}$, corresponding to the molecular ion of anthracene. As expected, fragmentation to give anthracene was especially pronounced; only weak molecular ions for the adducts were observed in each case. In contrast, the monocyclic adducts (173), (174), (176), (185), and (186) did not undergo retro-Diels-Alder fragmentation to any significant extent. This parallels the relative thermal stability of bridged and monocyclic thioaldehyde cycloadducts. It is not clear whether the retro-Diels-Alder cleavage observed in the mass spectra is induced by electron impact or is purely thermal. However, it provides a useful method for identifying the bridged class of adducts.

Sulphur-Containing Fragment Ions. The monocyclic adducts (173), (174), (176), (185), and (186), and the bicyclic lactone (191) all gave spectra having base peaks arising from sulphur-containing fragment ions. One ion in particular, $C_5H_5S^+$, formed the base peak for 3 of the

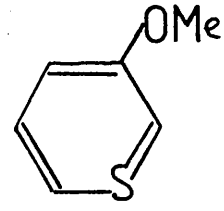
compounds and was a major fragment ion from the others. The aromatic, thiopyrylium structure (198) would account for the high abundance of this fragment. Similarly, the ion $C_5H_3OS^+$, which formed the base peak for the monocyclic adducts (173) and (174), may have the aromatic structure (199). Of course, both structural proposals are only tentative. Other sulphur-containing peaks arise from loss of small fragments from the molecular ions.



(198)

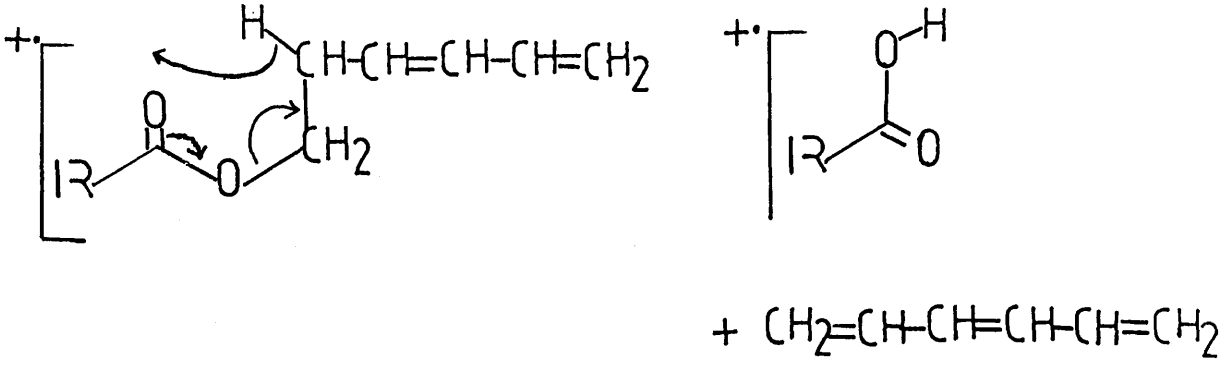


(199)



(200)

For example, the ethyl esters (173) and (174) lose, presumably, EtO, EtOH and EtO_2C; the diacid (176) loses H_2O and CO (or CO_2 and H_2); the methyl esters (185) and (186) lose MeOH; the anhydride (188) loses CO_2; and the hexadienyl ester (190) loses C_6H_8 by the characteristic[73] rearrangement fragmentation, Scheme 86. In the last



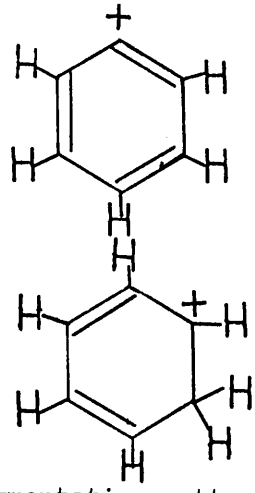
Scheme 86.

example, the ion $[RCO_2H]^{+\cdot}$, $C_{16}H_{12}O_2S$, may form the only other sulphur-containing fragment ion $C_{15}H_{12}S^{+\cdot}$, by loss of CO_2. It is more difficult to assign structures to the remaining sulphur-containing ions derived from the cycloadducts. However, some may be closely related to the stable ions (198), (199); for example the ion $C_6H_7OS^+$ derived from the esters (161) and (162) and the acids (163) and (164) may have the structure (200).

Sulphur-free Fragment Ions. Peaks for the hydrocarbon fragment ions $C_6H_7^+$, $C_6H_5^+$, and $C_5H_5^+$ were seen in the spectra of several of the cycloadducts. It has been suggested[74-77] that the benzene molecular ion $C_6H_6^{+\cdot}$ may exist in the open chain form (201). For this reason, the conjugated cations (202)-(204) are plausible candidates for the observed hydrocarbon fragmnet ions.

$[H-C\equiv C-CH=CH-CH=CH_2]^{+\cdot}$	$C_6H_6^{+\cdot}$	(201)
$H-C\equiv C-CH=CH-\overset{+}{C}H-CH_3$	$C_6H_7^+$	(202)
$H-C\equiv C-C\equiv C-\overset{+}{C}H-CH_3$	$C_6H_5^+$	(203)
$H-C\equiv C-CH=CH=\overset{+}{C}H_2$	$C_5H_5^+$	(204)
$H-C\equiv C-CH=CH-C\equiv\overset{+}{O}$	$C_5H_3O^+$	(205)

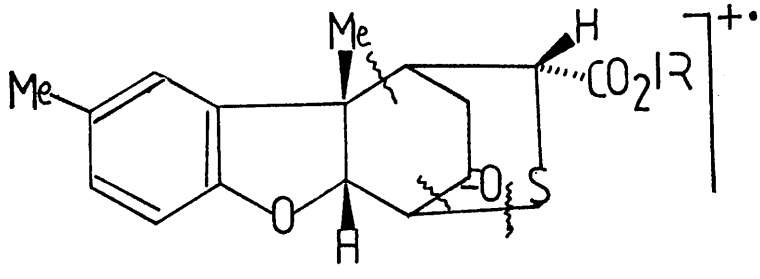
These would have to rise by cleavage of the six-membered rings, loss of heteroatoms, and rearrangement of hydrogens. Alternative, cyclic structure, for example (206) for $C_6H_5^+$ and (207) for $C_6H_7^+$, cannot be excluded. The ions $C_5H_3\overset{+}{O}$ observed in the spectra of the monocyclic adducts (173) and (174), and (176) and of the anthracene adduct (190), may have the common structure (205) arising from fragmentation of quite different structural units. Again, this would be reasonable only if the ion was specially stabilised as (205) would be by conjugation.



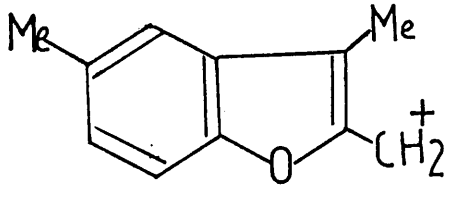
$C_6H_5^+$ (206)

$C_6H_7^+$ (207)

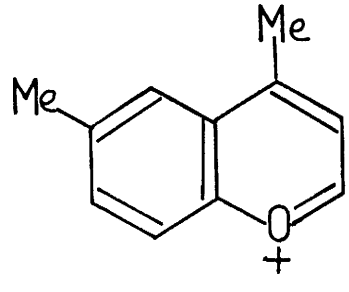
The fragmentation patterns for the ester (195) and acid (197) Table 12 and 13, derived from the dienamine of Pummerer's ketone were dominated by base peaks at m/z 159. The composition $C_{11}H_{11}O$ (supported by those of the corresponding ^{13}C peaks, m/z 160) and the high intensity of these peaks suggest stable structures such as (209) or (210). Clearly, several steps would be required to complete the fragmentation, but cleavage of bonds adjacent to the ketonic carbonyl group [see (208)], relieving strain in the bridged ring system, is reasonable. Cleavage of one more bond leading to a



(208)



(209)

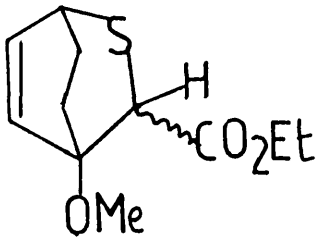


(210)

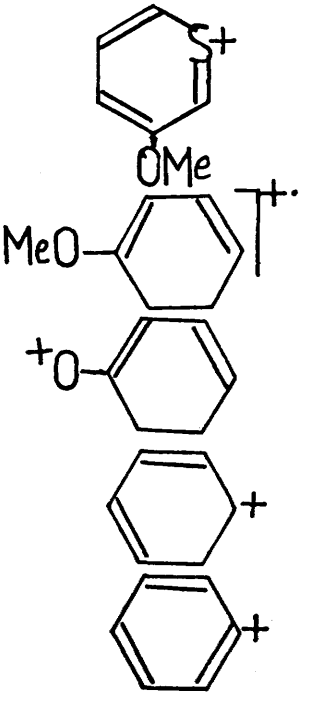
tertiary, benzylic carbon, and 1,2-migration of hydrogen would produce

the cation (209). Alternatively a 1,2-shift of the tertiary carbon would lead to (210).

Table 3. Mass Spectra of the Endo and Exo Isomers of 4-Methoxy-2-thiabicyclo[2.2.2]oct-5-ene-3-carboxylate (161) and (162)



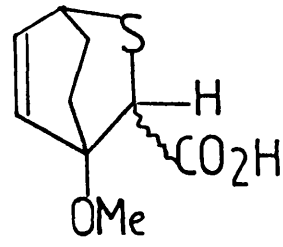
m/z (161) and (162)

Found	Calculated	% Basepeak	Composition	Constitution
228.0816[a]	228.0821	3.6	$C_{11}H_{16}O_3S$	M^+
228.0815[b]	228.0820	2.8		
185.0637[a]	185.0637	4.5	$C_9H_{13}O_2S$	$M-C_2H_3O$
181.0864[a]	181.0865	14.9	$C_{10}H_{13}O_3$	$M-CH_3S$
155.0525[b]	155.0531	3.9	$C_8H_{11}OS$	$M-C_3H_5O_2$
127.0216[a]	127.0217	7.7	C_6H_7OS	
127.0221[b]	127.0217	5.3		
110.0725[a]	110.0732	100	$C_7H_{10}O$	
110.0724[b]	110.0731	100		
95.0495[a]	95.0497	24.3	C_6H_7O	
95.0491[b]	95.0497	16.6		
79.0546[a]	79.0547	16.4	C_6H_7	
79.0549[b]	79.0547	11.4		
77.0393[a]	77.0391	12.5	C_6H_5	
77.0386[b]	77.0391	8.7		

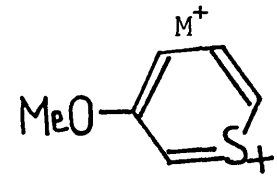
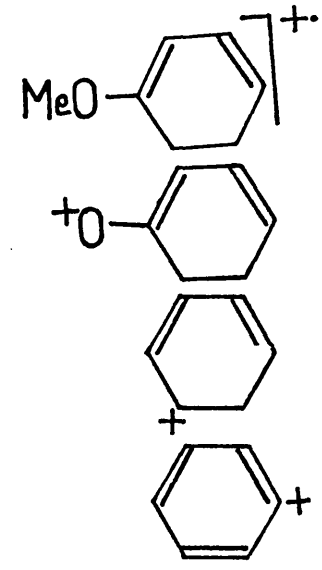
[a] Endo isomer (161)

[b] Exo isomer (162)

Table 4. Mass Spectra of the Endo and Exo Isomers of 4-Methoxy-2-thiabicyclo [2.2.2] oct-5-ene-3-carboxylic acid (163) and (164)



(163) and (164)

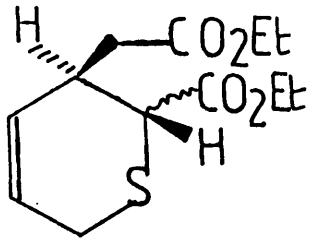
Found	Calculated	% Basepeak	Composition	Constitution
200.0510[a]	200.0507	2.3	$C_9H_{12}O_3S$	
200.0520[b]	200.0507	0.9		
127.0213[a]	127.0217	4.7	C_6H_7OS	
127.0219[b]	127.0217	3.8		
110.0733[a]	110.0731	100	$C_7H_{10}O$	
110.0720[b]	110.0731	100		
95.0494[a]	95.0497	22.8	C_6H_7O	
95.0496[b]	95.0497	12.2		
79.0541[a]	79.0547	14.1	C_6H_7	
79.0548[b]	79.0548	7.5		
77.0376[a]	77.0391	11.3	C_6H_5	
77.0388[b]	77.0391	6.0		

[a] Endo isomer (163)

[b] Exo isomer (164)

Table 5. Mass spectrum of the Mixture of the Diethyl 3,6-Dihydro-3-methyl-2H-thiin-2,7-dicarboxylates (173) and (174)

(cis:trans, 3:1)



(173) and (174)

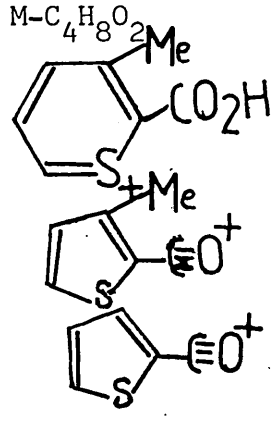
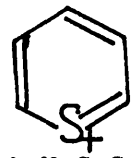
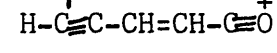
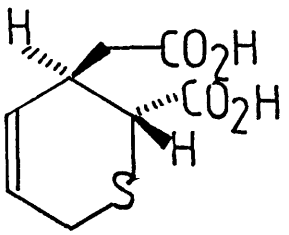
Found	Calculated	% Basepeak	Composition	Constitution
258.0928	258.0926	13.5	$C_{12}H_{18}O_4S$	M^+
225.1112	225.1127	0.8	$C_{12}H_{17}O_4$	M-SH
213.0575	213.0586	8.6	$C_{10}H_{13}O_3S$	$M-C_2H_5O$
212.0513	212.0507	20.8	$C_{10}H_{12}O_3S$	$M-C_2H_6O$
185.0626	185.0636	15.59	$C_9H_{13}O_2S$	$M-C_3H_5O_2$
170.0402	170.0401	48.0	$C_8H_{10}O_2S$	$M-C_4H_8O_2$
155.0153	155.0167	11.6	$C_7H_7O_2S$	
125.0071	125.0069	15.3	C_6H_5OS	
110.9881	110.9905	36.4	C_5H_3OS	
97.0132	97.0112	100	C_5H_5S	
79.0168	79.0184	15.4	C_5H_3O	

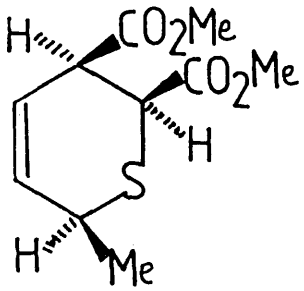
Table 6. Mass Spectrum of trans-3,6-Dihydro-3-methyl-2-H-thiin-2,7-dicarboxylic Acid (176).



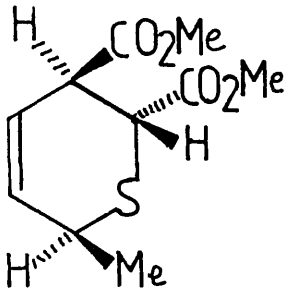
(176)

Found	Calculated	% Basepeak	Composition	Constitution
202.0305	202.0300	9.6	$C_8H_{10}O_4S$	$M^{+\bullet}$
184.0203	184.0195	14.2	$C_8H_8O_3S$	$M-H_2O$
156.0241	156.0245	5.2	$C_7H_8O_2S$	$M-H_2O-CO$
110.9880	110.9905	17.5	C_5H_3OS	
97.0126	97.0112	100	C_5H_5S	
79.0169	79.0164	15.4	C_5H_3O	$HC\equiv C-CH=CH-C\equiv O^{+}$

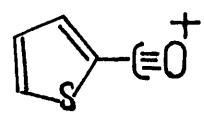
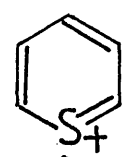
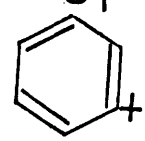
Table 7. Mass spectra of the Cis-Cis and Trans-Cis Isomers of Dimethyl 6-Methyl-1-thiocyclohex-4-ene-2,3-dicarboxylate (185) and (186).



(185)



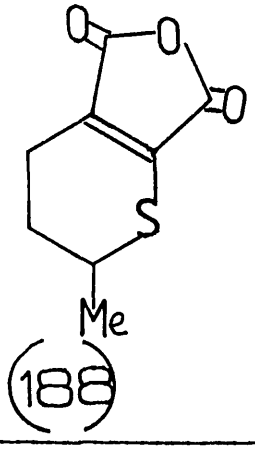
(186)

Found	Calculated	% Basepeak	Composition	Constitution
230.0614[c]	230.0613	24.5	$C_{10}H_{14}O_4S$	$M^{+\cdot}$
230.0618[t]	230.0613	3.9		
198.0353[c]	198.0351	23.8	$C_9H_{10}O_3S$	$M-CH_3OH]^{+\cdot}$
198.0369[t]	198.0350	1.6		
169.0328[c]	169.0323	17.9	$C_8H_9O_2S$	$M-C_2H_5O_2]^{+}$
169.0321[t]	169.0323	2.5		
155.0165[c]	155.0167	48.9	$C_7H_7O_2S$	$M-C_3H_7O_2]^{+}$
155.0179[t]	155.0167	2.6		
139.02229[c]	139.0218	19.8	C_7H_7OS	$M-C_3H_7O_3]^{+}$
127.0225[c]	127.0217	16.6	C_6H_7OS	$M-C_4H_7O_3]^{+}$
127.0217[t]	127.0218	9.5		
110.9876[c]	110.9904	100	C_5H_3OS	
110.9898[t]	110.9905	100		
97.0124[c]	97.0112	20.3	C_5H_5S	
97.0125[t]	97.0112	9.9		
77.0383[c]	77.0391	16.9	C_6H_5	
77.0377[t]	77.0391	5.1		

[c] Values for the major isomer (185)

[t] Values for the minor isomer (186)

Table 8. Mass spectrum of 6-Methyl-1-thiocyclohex-2-ene-dicarboxylic Acid Anhydride (188)



(188)

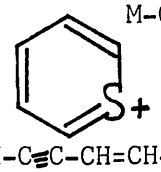
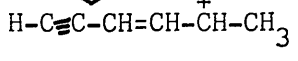
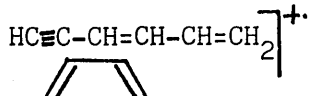
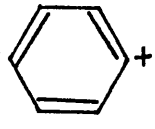
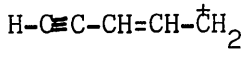
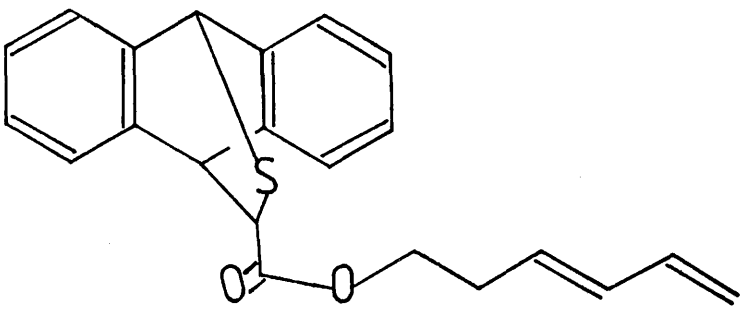
Found	Calculated	% Basepeak	Composition	Constitution
184.0187	184.0191	100	$C_8H_8O_3S$	$M^{+\bullet}$
140.0306	140.0296	63.5	C_7H_8OS	$[M-CO_2]^{+\bullet}$
97.0134	97.0112	26.9	C_5H_5S	
79.0553	79.0547	31.5	C_6H_7	
78.0485	78.0470	6.6	C_6H_6	
77.0401	77.0392	10.9	C_6H_5	
65.0392	65.0392	2.4	C_5H_5	
43.9721	43.9721	14.6	CS	CS^{+}

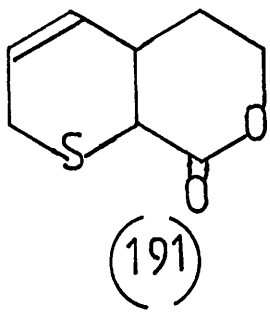
Table 9. Mass Spectrum of trans-Hexa-3,5-dien-1-yl 9,10-Dihydro-10,9-thioethaneoanthracene-12-carboxylate (190).



(190)

Found	Calculated	% Basepeak	Composition	Constitution
348.1202	348.1184	0.2	$C_{22}H_{20}O_2S$	$M^{+\bullet}$
268.0547	268.0558	0.6	$C_{16}H_{12}O_2S$	
223.0591	223.0582	0.4		
205.0651	205.0653	0.5		
178.0775	178.0782	100	$C_{14}H_{10}$	anthracene$]^{+\bullet}$
79.0171	79.0184	3.8	C_5H_3O	$H-C\equiv C-CH=CH-C\equiv O^{+}$

Table 10. Mass Spectrum of 7-Thio-4-oxobicyclo[4.4.0]dec-9-ene-5-one (191)



(191)

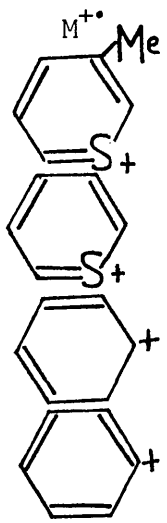
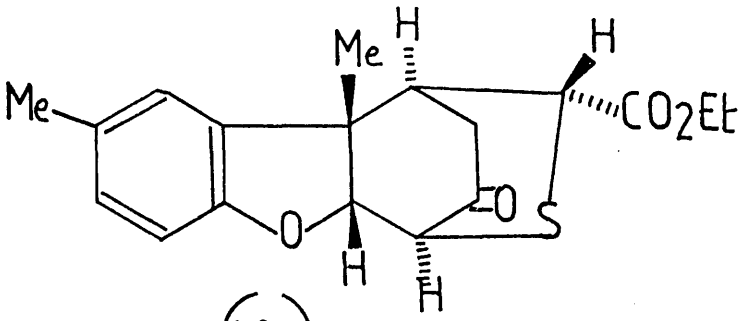
Found	Calculated	% Basepeak	Composition	Constitution
170.0408	170.0401	65.8	$C_8H_{10}O_2S$	
111.0249	111.0269	27.4	C_6H_7S	
97.0107	97.0112	100	C_5H_5S	
79.0526	79.0548	21	C_6H_7	
77.0376	77.0391	16.7	C_6H_5	

Table 11. Mass Spectrum of Ethyl 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylate (195)



(195)

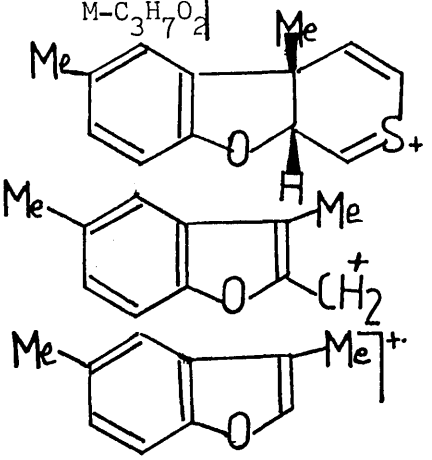
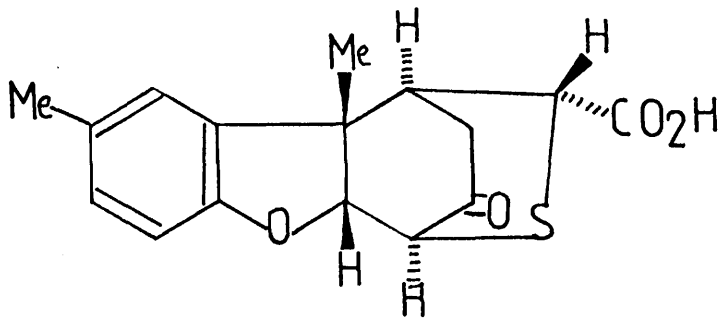
Found	Calculated	% Basepeak	Composition	Constitution
332.1079	332.1082	9.3	$C_{18}H_{20}O_4S$	$M^{+\cdot}$
317.0842	317.0847	0.15	$C_{17}H_{17}O_4S$	$M-CH_3]^+$
259.0796	259.0793	1.6	$C_{15}H_{15}O_2S$	$M-C_3H_5O_2]^+$
257.0637	257.0637	0.7	$C_{15}H_{13}O_2S$	$M-C_3H_7O_2]^+$
217.0679	217.0687	0.7	$C_{13}H_{13}OS$	
159.0812	159.0810	100	$C_{11}H_{11}O$	
146.0731	146.0732	7.7	$C_{10}H_{10}O$	

Table 12. Mass Spectrum of 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylic Acid (197)



(197)

Found	Calculated	% Basepeak	Composition	Constitution
304.0773	304.0769	7.6	$C_{16}H_{16}O_4S$	$M^{+\bullet}$
215.0511	215.0521	0.7	$C_{13}H_{11}OS$	$M-C_3H_5O_3$
214.0993	214.0994	2.1	$C_{14}H_{14}O_2$	
159.0809	159.0810	100	$C_{11}H_{11}O$	
146.0727	146.0731	11.3	$C_{10}H_{10}O$	

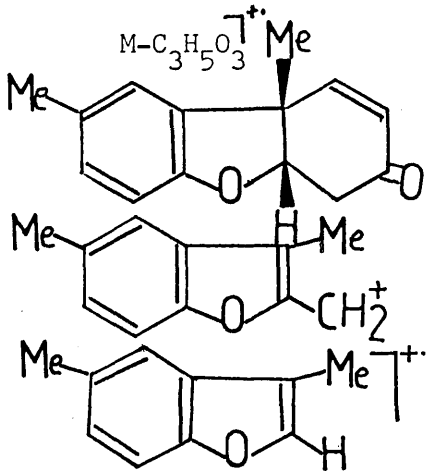
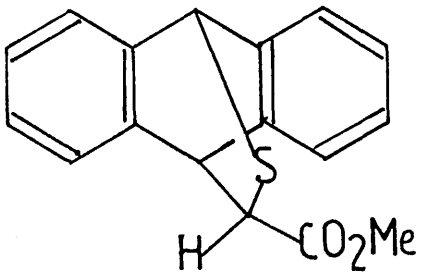


Table 13. Mass Spectrum of Methyl 9,10-Dihydro-10,9-thioethanoanthracene-12-carboxylate (184)



(184)

Found	Calculated	% Basepeak	Composition	Constitution
282.0722	282.0715	3.7	$C_{17}H_{14}O_2S$	$M^{+\bullet}$
178.0789	178.0782	100	$C_{14}H_{10}$	anthracene$]^{+\bullet}$

CHAPTER FOUR.

EXPERIMENTAL

Instrumentation and General Notes:- Melting points, which are uncorrected, were determined on a Kofler hot-stage apparatus. Microanalyses were obtained by Mrs. W. Harkness and her staff. Low resolution mass spectra were recorded at 70 ev on an A.E.I. M.S.12 instrument and high resolution spectra on an A.E.I. M.S. 9 instrument coupled to a GEC-905 Computer for data collection and processing. Infra-red spectra were recorded on either a Perkin-Elmer 580 or 257 spectrometer by Mrs. F. Lawrie and her staff. ^{1}H n.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R.32 instrument. 200 MHz spectra were recorded on a Bruker WP 200 SY instrument in the pulsed Fourier Transform (F.T) mode by Dr. D.S. Rycroft; chemical shifts are quoted as p.p.m. down field from tetramethylsilane.

Analytical t.l.c. was carried out on precoated Merck Kieselgel GF_{254} plates of thickness 0.25 mm. Spots were viewed under an ultra-violet lamp (254 nm) and developed by iodine vapour. Column chromatography was carried out on Merck silica HF_{254} under reduced pressure according to the method of Targett et al.[78] Preparative plate chromatography was carried out on Merck GF_{254} silica with detection of compounds by u.v.light.

All solvents and reagents used were of analytical grade unless otherwise stated. 'Light petroleum' refers to the fraction b.p. 60-80^{o}C. 'Ether' refers to diethyl ether.

Stirring of reaction media was carried out using magnetic stirrer bars.

Organic solutions were dried over anhydrous magnesium sulphate and evaporated on a Buchi rotary evaporator under water-pump vacuum.

The following abbreviations and symbols have been used in this thesis:

b.	broad
d.	doublet
m.	multiplet
q.	quartet
p.	pentuplet
s.	singlet
t.	triplet
i.r.	infra-red
n.m.r.	nuclear magnetic resonance
t.l.c.	thin layer chromatography
h	han
min	minute
Hz	Hertz

Preparation of Ethyl 4-Methoxy-2-Thiabicyclo[2.2.2]oct-5-ene-3-carboxylate (161) and (162):-

The Bunte salt (151a) (1.73g, 7.75 mmol) and calcium chloride dihydrate (1.15g, 7.75 mmol) were dissolved in ethanol (30ml). 1-Methoxy-1,3-cyclohexadiene (160) (1.22g, 7.75 mmol) [the diene was purchased from Aldrich Chemical Co Ltd. and used as a mixture of 1-methoxy-1,3-cyclohexadiene (70%) and 1-methoxy-1,4-cyclohexadiene (30%); the quantities cited are those corresponding to 1,3-diene] was added in benzene (25ml) to the salt mixture. Triethylamine (0.79g, 7.75 mmol) in benzene (2ml) was then added. The reaction mixture was stirred at room temperature for 5 days then was diluted with analar chloroform (50ml) and water (30ml). Dilute (5%) hydrochloric acid was added until the calcium sulphite had dissolved and the mixture had become clear. The organic layer was washed with aqueous sodium bicarbonate to remove the excess of hydrochloric acid, then it was washed with brine (10ml), water (20ml), and was dried ($MgSO_4$) and evaporated to afford a mixture of the cycloadducts (161)

and (162) (1.50g, 60%) was a yellow oil. This mixture was chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (80:20) gave the two cycloadducts (1.42g, 56.8%) as a yellow oil. The ^1H n.m.r. spectrum showed the presence of the endo (161) and exo (162) isomers in the ratio of 4:1 based upon integration of the olefinic proton signals. The two isomers were separated on silica plates developed three times with light petroleum-ether (80:20) to afford the pure isomers (161) and (162) (ratio 4:1), the latter having the higher R_F value. The major product, ethyl 4-methoxy-2-thiabicyclo[2.2.2] oct-5-ene-3-endo-carboxylate (161), was obtained as an oil (Found: m/z 228.0816. $C_{11}H_{16}O_3S$ requires M, 228.0821; ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ ($CDCl_3$, 90 MHz) 1.27 (t, J 7.0Hz, OCH_2CH_3), 1.55-2.47 (m, 7- and 8-CH_2), 3.43 (S, 4-OCH_3), 3.52 (m, 1-H), 4.14 (S, 3-H), 4.19 (q, J 7.0Hz, OCH_2CH_3) and 6.20-6.75 (m, 5- and 6-H). The minor product, ethyl 4-methoxy-2-thiabicyclo[2.2.2] oct-5-ene-3-exo-carboxylate (162), was obtained as an oil. (Found: m/z 228.0815. $C_{11}H_{16}O_3S$ requires M, 228.0821; ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ ($CDCl_3$, 90 MHz) 1.30 (t, J 7.0Hz, OCH_2CH_3), 1.50-2.80 (m, 7- and 8-CH_2), 3.5 (s, 4-OCH_3), ca. 3.5 (m, 1-H), 3.83 (s,3-H), 4.28 (q, J 7.0Hz, OCH_2CH_3), and 6.30-6.70 (m,7- and 8-CH_2).

Hydrolysis of the endo-ester (161):- 1.03M sodium hydroxide (7ml) was added to a solution of the foregoing endo-ester (161) (0.40g, 1.75mmol) in tetrahydrofuran (5ml) and the mixture was stirred at room temperature overnight. After 24h the solution was concentrated under reduced pressure with heating. The resulting aqueous solution was washed with ether (5x20ml), then acidified with 5% hydrochloric acid (10ml) and extracted with ether (5x20ml). The ethereal extracts were washed with brine (10ml), dried ($MgSO_4$), and evaporated under reduced oressure with slight heating to give the pure 4-methoxy-2-thiabicyclo[2.2.2]oct-5-ene-3-endo-carboxylic acid (163) (0.31g, 90%), m.p. 114-115°C (from

hexane) (Found: C,54.00; H, 6.30; S, 16.30. $C_9H_{12}O_3S$ requires C,53.98; H, 6.00; S, 16.01%) (Found: m/z, 200.0510. $C_9H_{12}O_3S$ requires M 200.0507); ν_{max} (KBr) 1725 cm^{-1}; $\delta(CDCl_3$, 200 MHz) 2.24 (1H, m) and 1.62-1.92 (3H, m) (7- and 8-CH_2), 3.46 (S, 40 Me), 3.53 (dtd, J 6.8, 2.7, and 0.9 Hz, 1-H), 4.12 (d, J 0.8 Hz, 3-H), 6.22 (dd, J 8.9 and 0.7 Hz, 5-H), and 6.60 (dd, J 8.9 and 6.8 Hz, 6-H), 9.75 (bS, CO_2H, exch. with D_2O).

Hydrolysis of the exo-ester (164):- The exo-ester (162) (0.22g, 1.1 mmol) was hydrolysed as described for the endo isomer to give 4-methoxy-2-thiabicyclo[2.2.2] oct-5-ene-3-exo-carboxylic acid (164) (0.169g, 88%), m.p. 124-125°C (from hexane) (Found: C,54.01; H, 6.12; S, 16.20.$C_9H_{12}O_3S$ requires C,53.98; H, 6.04; S, 16.01%) (Found: m/z 200.0520. $C_9H_{12}O_3S$ requires M, 200.0507); ν_{max} (KBr) 1705 cm^{-1}; $\delta(CDCl_3$, 200 MHz) 2.28-2.45 (2H, m), 1.76-1.94 (1H, m), and 1.57 (1H, ddd, J 12.0, 8.0 and 2.0Hz) (7- and 8-CH_2), 3.50 (S, 4-OMe), ca. 3.5 (m, 1-H), 3.84 (d, J 2.2Hz, 3-H), 6.36 (d, J 8.9Hz, 5-H), and 6.60 (dd, J 8.9 and 6.8Hz, 6-H), 8.52 (bs, CO_2H, exch. with D_2O).

Preparation of Ethyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (141a).

Following the literature method[56], ethyl mercaptoacetate was converted in benzene into the corresponding sulphenyl chloride (136) using N-chlorosuccinimide (13.2 mmol). This was added to anthracene (55 mmol) and triethylamine (13.2 mmol), as described before, to give the cycloadduct (141a) (35%), m.p. 135-137°C (from ether); the ^1H n.m.r. spectrum agreed well with that reported[56].

Hydrolysis of Ethyl 9,10-Dihydro-10,9-thiaethano-anthracene (141a).

The ester (141a) (0.50g, 1.68 mmol) in tetrahydrofuran (10ml) was stirred with aqueous sodium hydroxide (1.03M, 10ml) at room temperature overnight. The mixture was evaporated under reduced pressure with heating. The aqueous solution was washed with dichloromethane (5x30ml), then acidified with 5% hydrochloric acid (10ml) and extracted with ether (5x30ml). The ethereal extracts were then washed with brine (10ml), dried ($MgSO_4$), and evaporated under reduced pressure with slight heating to give the pure acid (183) (0.35g, 78%), m.p. 182-184°C (from ether). The ^1H n.m.r. spectrum was identical with that of a sample of the acid prepared[79] by S.M.Choi.

Esterification of 9,10-Dihydro-10,9,thiaethano-anthracene-12-carboxylic acid (183).

The acid (183) (0.50g, 1.86 mmol) in magnesium-dried ethanol (10ml) was treated with acetyl chloride (0.785g, 10mmol) dropwise. The reaction mixture was kept dry with a guard tube containing silica gel. The mixture was stirred at room temperature overnight then was evaporated under reduced pressure with slight heating to give the ethyl ester (141a) (0.523g, 93%), m.p. 135-137°C (from ether). The ^1H n.m.r. spectrum agreed well with that reported[56].

Improved Preparation [79] of 9,10-Dihydro-10,9-thiaethano-anthracene-12-Carboxylic Acid (183).

The following procedure was developed by S.M. Choi and R.A. Lewis. Ethyl mercaptoacetate (1.32g, 11 mmol) was added dropwise with stirring to a suspension of N-chlorosuccinimide (1.76g, 13.2 mmol) in benzene (20ml) at room temperature. A yellow colour, signifying the formation of the sulphenyl chloride (136), developed after a while.

After 2.5h the solution of the sulphenyl chloride was added dropwise, by a glass syringe, with stirring to anthracene (9.80g, 55 mmol) and triethylamine (1.33g, 13.2 mmol) in Analar chloroform (140ml) with heating under reflux. 30 minutes after the last addition of sulphenyl chloride solution, the mixture was cooled and the excess of anthracene was filtered off. The filtrate was washed with dilute hydrochloric acid (10ml), then water (2x20ml), and was dried ($MgSO_4$) and evaporated under reduced pressure with heating. The residue was dissolved in tetrahydrofuran (THF) (15ml) and stirred with aqueous sodium hydroxide (1.03M, 15ml) at room temperature. After 7h, the THF was evaporated under reduced pressure with heating. The aqueous solution was washed with dichloromethane (5x30ml), then acidified with 5% hydrochloric acid (15ml) and extracted with ether (5x30ml). The ethereal extracts were then washed with brine (10ml) dried ($MgSO_4$), and evaporated under reduced pressure with slight heating. The residue of substantially pure acid (1.98g, 7.38 mmol, 67% yield from ethyl mercaptoacetate) was chromatographed on a silica column (HF_{254}), and eluted with chloroform-light petroleum (2:8) then chloroform. Crystallisation from ether gave the carboxylic acid (183) (1.16g, 4.32 mmol, 39.2% yield from ethyl mercaptoacetate), m.p. 182-184°C. The ^1H n.m.r. spectrum of the acid was essentially identical with that of material prepared as described above.

Thermal Transfer of Ethyl Thioxoacetate from the Anthracene Cycloadduct to 1-Methoxy-1,3-cyclohexadiene.

The anthracene cycloadduct (141a) (0.50g, 1.69 mmol) and 1-methoxy-1,3-cyclohexadiene (0.235g, 1.3 mol equiv.) [the diene was purchased from Aldrich Chemical Co. Ltd. and used as a mixture of 1-methoxy-1,3-cyclohexadiene (70%) and 1-methoxy-1,4-cyclohexadiene (30%), the quantities cited are those corresponding to 1,3-diene] were

heated in redistilled toluene (10ml) under reflux for 4h. The toluene was evaporated under reduced pressure with heating to give a crude mixture (0.737g) that was shown by ^{1}H n.m.r spectroscopy to contain the cycloadduct (161) and (162). The mixture was then chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (70:30) then chloroform gave the cycloadduct (161) and (162) (0.26g, 67.5%) as a yellow oil; endo:exo ratio 4:1 . The two isomers were separated on silica plates developed three times with light petroleum-ether (80:20). The ^{1}H n.m.r. spectrum of each isomer agreed well with that of the compound obtained from the Bunte Salt (151a).

Hydrolysis of the endo-ester (161) and exo-ester (162) Obtained from the Transfer Reaction.

The ester (161) (0.49g, 2.15 mmol) was hydrolysed with aqueous sodium hydroxide in tetrahydrofuran, as described before, to give the acid (163) (0.34g, 80%), m.p. 114-115^{o}C (from hexane). Similarly the ester (162) (0.056g, 0.245 mmol) gave the acid (164) (0.041g, 83.4%), m.p. 124-125^{o}C (from hexane). The ^{1}H n.m.r. spectrum of each isomer agreed well with that of the compound obtained from the Bunte Salt (151a).

Esterification of 4-Methoxy-2-thiabicyclo[2.2.2] oct-5-ene-3-endo-carboxylic acid (163).

The acid (163) (0.22g, 0.96mmol) in dry ethanol (10ml) was treated dropwise with redistilled acetyl chloride (0.785g, 1.00mmol). The mixture was kept at room temperature overnight, guarded by a drying tube. The solvents were evaporated under reduced pressure with heating to give the endo-ester (161) (0.23g, 92%) as a yellow oil. The ^{1}H

n.m.r. spectrum (90 MHz) showed that esterification had occurred without epimerisation.

Thermal Isomerisation of the endo-ester (161).

The pure endo-ester (161) (0.20g, 0.88 mmol), prepared as described above from the pure acid (163), was heated in redistilled toluene (10ml) under reflux overnight. The toluene was evaporated under reduced pressure with heating to give a complex oily mixture (0.19g). The ^{1}H n.m.r. spectrum showed the presence of some endo-ester (161), some exo-ester (162), and other unidentified products.

Attempted Thermal Isomerisation of the endo-ester (161) in Benzene.

The pure endo-ester (161) was unchanged after being heated under reflux in benzene for 1.5h.

Attempted Thermal Isomerisation of the endo-ester (161) in Ethanol.

The pure endo-ester (161) was unchanged after being heated in dry ethanol under reflux for 1h.

Attempted Bromolactonisation of the endo and exo-acids (163) and (164).

The mixture of acids (163) and (164) (0.12g, 0.60 mmol) was dissolved in 5% aqueous sodium carbonate (5ml). Bromine-water was added dropwise with stirring at room temperature until the colour of bromine persisted. The mixture was extracted with chloroform, and the extract was dried ($MgSO_4$) and evaporated to give a gum (0.80g). The ^{1}H n.m.r. spectrum showed no signal for a methoxy group.

Epimerisation of Ethyl 4-Methoxy-2-thiabicyclo[2.2.2] oct-5-ene-3-endo-carboxylate (161).

The endo-ester (161) (0.109g, 0.48 mmol), prepared from the pure acid (163), was heated under reflux in sodium ethoxide (10ml, 0.1M) for 1h. The mixture was diluted with analar chloroform (30ml), then acidified with 5% hydrochloric acid, and extracted with chloroform. The extracts were washed with aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated under reduced pressure with heating to give a mixture (0.106g) of the endo (161) and exo (162) isomers in the ratio of 6:4, as judged from integration of the ^1H n.m.r. spectrum. The two isomers were separated on silica plates developed with light petroleum-ether (80:20). Each isomer was hydrolysed with sodium hydroxide to give the corresponding acid, which gave the appropriate m.p. and mixed m.p.

Epimerisation of the mixture (4:1) of the endo (161) and exo-esters (162).

The mixture of esters (0.124g, 0.54 mmol) was heated under reflux in sodium ethoxide (10ml, 0.1M) overnight. The reaction mixture was worked-up as before to give a mixture (0.116g) of the esters, endo:exo ratio, 6:4.

Preparation[80] of Sorboyl Chloride (212).

Thionyl chloride (13ml) was added over 1.5h to a warm (60°C) solution of sorbic acid (211) (5.6g, 0.05 mol) in benzene (160ml). After the mixture had been heated under reflux for 16h, material boiling up to 81°C was removed by distillation at atmospheric pressure. Fractionation of the brown residue gave sorboyl chloride (212), b.p. 75°C (20 mm Hg), whose ^1H n.m.r. spectrum agreed with that reported[80] in literature.

Preparation[81] of Ethyl 3,5-Hexadienoate (172).

Freshly distilled sorboyl chloride (212) (3ml, 23 mmol) was added dropwise to a cooled ('dry-ice'-acetone) solution of dry thanol (2.67ml, 45.9 mmol) and triethylamine (6.37ml, 45.9 mmol) in analar dichloromethane (45ml). After 45 min., a thick precipitate appeared. The reaction mixture allowed to warm to room temperature and after 4h was partitioned between water and dichloromethane. The organic layer was washed (twice with aqueous sulphuric acid, once with saturated sodium hydrogen carbonate, once with water, and once with brine), dried ($MgSO_4$), and concentrated. A few crystals of 2,6-di-tert-butyl-4-methyl phenol were added to the crude product whicn was then distilled, b.p. 40°C (1.5mm Hg), to afford the dienes (172) and (172a) (5g, 77%), in a ratio of 9:1 respectively, as a colourless liquid whose ^1H n.m.r. spectra were in agreement with those reported[82].

Preparation of the Cycloadduct (173) and (174) of Ethyl Thioxoacetate and the Hexadienoate (172).

The Bunte salt (151a) (0.476g, 2.14 mmol) and calcium chloride dihydrate (0.315g, 2.15 mmol) were dissolved in ethanol (10ml). Ethyl 3,5-hexadienoate (172) (0.3g, 2.14 mmol) was added in benzene (8ml) to the mixture of salts followed by triethylamine (0.217g, 2.14 mmol) also in benzene (2ml). The reaction mixture was stirred at room temperature for 3 days, then it was diluted with analar dichloromethane (30ml) and water (20ml). Dilute hydrochloric acid (5%) was added until the mixture became clear. The organic layer was washed with aqueous sodium bicarbonate to remove the excess of hydrochloric acid, then with brine (10ml), water (20ml), and was dried ($MgSO_4$) and evaporated to give the cycloadducts (173) and (174) (0.468g). The mixture was chromatographed on a short column of silica (HF_{254}).

Elution with light petroleum-chloroform (50:50) gave the two isomers (173) and (174) (0.312g, 56.5%) in a ratio of 3:1 (cis:trans) as determined by integration of the ^{1}H n.m.r. signals for 2-H. The mixture of cycloadducts (173) and (174) (Found: m/z 258.0928. $C_{12}H_{18}O_4S$ requires M 258.0921) gave mass spectroscopic fragments for M-SH, M-EtO, M-EtOH, M-EtO$_2$C, M-$C_4H_8O_2$, C_7H_7S and C_5H_5S (see Table 5 in Chapter 3); ν_{max} ($CHCl_3$) 1730 cm^{-1} δ($CDCl_3$, 90 MHz) 5.6-6.1 (m,4- and 5-H), 4.0-4.4 (m, OCH_2CH_3), 3.75 (d, J 4Hz, trans 2-H), 3.45 (d, J 3 Hz, cis 2-H), 3.40 (m, cis 3-H), 3.18 (m, trans 6-CH_2), 2.49-2.65 (m, cis 7-CH_2), 1.24 (2xt, J 7 Hz, OCH_2CH_3). The mixture was separated on silica plates, developed several times with light petroleum-ether (80:20) to afford pure cis(173) and trans(174) isomers in the ratio of 3:1 respecrively, the latter having the higher R_F value. Diethyl 3,6-dihydro-3-methyl-2H-thiin-2,7-dicarboxylate (173) gave δ($CDCl_3$, 200 MHz) 5.89 (m, 5-H), 5.73 (m, 4-H), 4.16 (m,2xOCH_2CH_3), 3,40 (m, 3-H), 3.45 (d,J 3.1Hz, 2-H), 3.29 (dq, J 17.5 and 2.4 Hz, 6-H), 2.91 (dd, J 17.2 and 5.0Hz with fine coupling, 6-CH_2), 2.65 (dd, J 16.2 and 8.0Hz, 7-H), 2.49 (dd, J 16.2 and 5.8 Hz, 7-H), and 1.25 and 1.27 (2xt, J 7.0Hz, 2xOCH_2CH_3).

Diethyl 3,6-dihydro-3-methyl-2H-thiin-2,7-dicarboxylate (174) gave δ($CDCl_3$, 200 MHz) 5.86 (m, 5-H), 5.72 (m, 4-H), 4.10 (2xq, J 7.0Hz, 2xOCH_2CH_3), 3.75 (d,J, 4.4 Hz, 2-H), 3.18 (m, 3-H), 3.18 (m, 6-CH_2), 2.52 (dd, J.16.0 and 7.)Hz, 7-H), 2.46 (dd, J 16.0 and 7.0Hz, 7-H), and 1.24 and 1.26 (2xt, J 7Hz, 2xOCH_2CH_3).

The 3,6-Dihydro-3-methyl-2H-thiin-2,7-dicarboxylic acids (175) and (176). 20% aqueous sodium hydroxide (6ml) was added to the mixture (3:1) of diesters (173) and (174) (0.515g) in ethanol (3ml) and the mixture was boiled under reflux (N_2 atmosphere) for 4h. The solution was acidified to pH1 with 2M-hydrochloric acid and extracted with ether

(3x30ml). Concentration of the dried extracts gave the trans (176) and cis(175) acids (0.41g, 73.2%) in the ratio of 3:1 as determined by integration of the ^{1}H n.m.r signals for 2-H. The mixture gave $\delta(CD_3COCD_3)$, 90 Mhz, 5.85 (m,4- and 5-H), 3.87 (0.75H, d, J 4.0Hz, trans 2-H), 3.54 (0.25H, d, J 3.0Hz, cis 2-H), 3.10 (m, 3-H), 3.20 (m, 6-CH_2), 2.54 (m, 7-CH_2), and 7.95 (bs, COOH exch. with D_2O). The mixture of the esters (173) and (174) (0.335g) was again hydrolysed with 20% aqueous sodium hydroxide, as described before, to give an acidic product that crystallised to afford the pure trans diacid (176) (0.20g, 76%). 3,6-Dihydro-3-methyl-2H-thiin-2,7-dicarboxylic acid (176) had m.p. 166-167°C (from chloroform) (Found: C, 47.37; H, 4.86; S, 15.86. $C_8H_{10}O_4S$ requires C, 47.51; H, 4.98; S, 15.85%) (Found: m/z 202.0305. $C_8H_{10}O_4S$ requires M, 202.0300); ν_{max} (KBr) 1725 cm^{-1}, $\delta(CD_3COCD_3$, 200 MHz) 5.88 (m, 5-H), 5.78 (m, 4-H), 3.87 (d, J 4.4 Hz, 2-H), 3.18 (m, 6-CH_2), 3.10 (m, 3-H), 2.53 (d, J 7.5Hz, 7-CH_2), and 10.9 (bs, 2 x COOH).

Attempted Base-Catalysed Epimerisation of the Cycloadducts (173) and (174) of Ethyl Thioxoacetate and the Hexadienoate (172) At Room Temperature:

The mixture of cycloadducts (173) and (174) (3:1) (107mg, 0.415 mmol) was kept in 0.1M sodium ethoxide (10ml) at room temperature for 5 days. The mixture was diluted with analar chloroform (30ml), then acidified with 5% hydrochloric acid, and extracted with chloroform. The organic layer was washed with aqueous sodium hydrogen carbonate and was dried ($MgSO_4$) and evaporated under reduced pressure with heating to give the esters (173) and (174) (90mg) in the original ratio, as judged by ^{1}H n.m.r. spectroscopy.

With heating: The foregoing experiment was repeated but the

mixture of esters (173) and (174) (100mg) was heated under reflux for 1h in the ethanolic sodium hydroxide. The usual work-up gave an oily product (30mg) that gave a complex ^1H n.m.r. spectrum.

Attempted Preparation of the Anhydride from the Cycloadduct Diacids (175) and (176).

The diacids (175) and (176) (110mg, 0.55 mmol) were kept in acetic anhydride at room temperature for 4h. The mixture was evaporated under reduced pressure with heating to give a mixture (90mg) which, after chromatography on silica (HF_{254}) column gave starting material.

Preparation of the Cycloadducts (173) and (174) of Ethyl Thioxoacetate and the Hexadienoate (9) using 3 mol Equivalents of the Bunte Salt.

The Bunte salt (151a) (0.666g, 3 mmol) and calcium chloride dihydrate (0.441g, 3mmol) were dissolved in ethanol (20ml). Ethyl 3,5-hexadienoate (0.42g, 3mmol) was added in benzene (15ml) to the mixture of salts. Triethylamine (o0.303g, 3mmol) was added in benzene (2ml) to the mixture. The reaction mixture was stirred at room temperature overnight, the Bunte salt (151a), calcium chloride, and triethylamine (6mmol of each) were added. The mixture was stirred at room temperature for another 5 days, then was diluted with analar chloroform (50ml) and water (20ml). Hydrochloric acid (5%) was added until the mixture became clear. The organic layer was washed successively with aqueous sodium bicarbonate, brine (10ml), and water (20ml), and was dried ($MgSO_4$) and evaporated to give a mixture (0.96g) of cycloadducts and the disulphide $(EtO_2CCH_2S)_2$. This mixture was chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (50:50) gave the two cycloadducts

(173) and (174) (0.50g, 65%) as a yellow oil. The ^{1}H n.m.r. spectrum was identical with that of the mixture obtained using 1 mol equiv. of the Bunte salt (151a).

Attempted Preparation of the Cycloadducts of Methyl Thioxoacetate and Methyl Sorbate (182).

The Bunte salt (181) (2.47g, 11.88 mmol) and calcium chloride dihydrate (1.75g, 11.88 mmol) were dissolved in methanol (20ml). Methyl sorbate (0.50g, 3.96 mmol) was added in benzene (15ml) to the salt mixture. Triethylamine (1.20g, 11.88 mmol) in benzene (1ml) was added to the mixture, which was then stirred at room temperature for 4 days. The reaction mixture was diluted with chloroform (30ml) and water (30ml), then acidified with dilute hydrochloric acid until the mixture became clear. The organic layer was washed with aqueous sodium hydrogen carbonate, brine (10ml), and water (20ml) and was dried ($MgSO_4$) and evaporated under reduced pressure with slight heating. The residue contained methyl sorbate but no cycloadduct, as judged by ^{1}H n.m.r. spectroscopy.

Preparation of Methyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-Carboxylate (184).

The acid (183) (0.33g, 1.24 mmol) in dry methanol (10ml) was treated dropwise with acetyl chloride (0.785g, 10mmol). The reaction mixture was kept dry by using a guard tube containing silica gel. The mixture was stirred at room temperature overnight then was evaporated under reduced pressure with heating to give the desired ester (26) (0.34g). This was passed quickly in chloroform through a silica (HF_{254}) column to give the pure methyl ester (184) (0.329g, 95%), m.p. 147-148^{o}C (from ether) (Found: C, 72.32; H, 5.08; S, 11.6%;

m/z 282.0722. $C_7H_{14}O_2S$ requires C, 72.31; H, 5.00; S, 11.36%; M, 282.0710); ν_{max} ($CHCl_3$) 1740 cm^{-1}; δ ($CDCl_3$, 90 MHz) 3.55 (s, OMe), 4.10 (d, J 3Hz, $SCHCO_2Me$), 5.05 (d, J 3Hz, 9-H), 5.05 (S, 10-H), and 7.09-7.45 (m, Ar-H).

Thermal Transfer of Methyl Thioxoacetate from the Anthracene Adduct (184) to Methyl Sorbate.

The anthracene adduct methyl ester (184) (0.273g, 0.97mmol) and methyl sorbate (0.121g, 0.97 mmol), in redistilled toluene (20ml), were heated under reflux overnight. The mixture was evaporated under reduced pressure with heating. The ^1H n.m.r. spectrum of the residue showed the formation of cycloadducts. The residue was treated with a small amount of chloroform and the excess of anthracene was filtered off. The filtrate was tnen chromatographed on a silica (HF_{254}) column. Elution with chloroform-light petroleum (30:70) then chloroform gave the desired cycloadducts (0.179g, 81%) as a mixture of the cis cis (185) and trans cis-isomer(186) in a ratio of 3:2 as judged from the n.m.r. signal of 2-H. The two isomers were separated on preparative silica t.l.c. plates developed several times with chloroform-light petroleum (30:70) to give the pure isomers in the ratio of 3:2 cis:trans. The major, cis cis-isomer (185) (Found: m/z 230.0614. $C_{10}H_{14}O_4S$ requires M, 230.0613) gave ν_{max}($CHCl_3$) 1735 cm^{-1}; δ($CDCl_3$, 90 MHz) 1.33 (d, J 7 Hz, 6-CH_3), 3.30-3.90 (m, 6- and 3-H), 3.75 (S, "xCO_2CH_3), 4.11 (d, J 5.0 Hz, 2-H), and 5.90 (bs, 4- and 5-H). The minor trans cis-isomer (186) (Found: m/z 230.0618. $C_{10}H_{14}O_4S$ requires M, 230.0613) gave ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ($CDCl_3$, 90 MHz) 1.30 (d, J 7.0Hz, 6-CH_3), 3.30-3.99 (m, 6- and 3-H), 3.70 and 3.75 (2xS, 2xCO_2CH_3), 3.95 (d, J 4.0Hz, 2-H), 5.80 (dm, J 10Hz, 4- or 5-H), 6.15 (dm, J 10Hz, 4- or 5-H).

Hydrolysis of Dimethyl 6-Methyl-1-thiacyclohex-4-ene-2,3-dicarboxylate (185) and (186).

20% aqueous sodium hydroxide (0.654ml) was added to a solution of the diester (185) and (186) (0.060g, 0.26 mmol) in ethanol (1 ml) and the mixture was boiled under reflux (N_2 atmosphere) for 4h. The solution was acidified to pH1 with 2M-hydrochloric acid and extracted with ether (4x30ml). Evaporation of the dried ($MgSO_4$) extract gave the diacid (187) (0.045g, 85%); δ(CD_3COCD_3, 90 MHz) 1.43 (d, J 6.5Hz, 6-CH_3), 1.5-2.4 (m, 5-CH_2), 2.60 (t, 6.0Hz, 4-CH_2), 3.60 (m, 6-H), 5.2 (br.S, 2xCOOH, exch. with D_2O).

Preparation of the Anhydride (188) from the diacid (187).

The dicarboxylic acid (187) (0.040g, 0.20mmol) was distilled (Kugelrohr distillation 120°C/0.1mm Hg) to give the anhydride (188) (0.025g, 0.136 mmol) (Found: m/z 184.0187 (basepeak). $C_8H_8O_3S$ requires M, 184.0191); ν_{max}($CHCl_3$) 1850 (weak band) and 1775 cm^{-1} (strong band); δ($CDCl_3$, 90 MHz) 1.44 (d, J 7.0Hz, Me), 1.5-2.0 (m, 5-CH_2), 2.57 (m, 4-CH_2), 3.42 (m, 6-H).

Preparation [82] of Hexa-3,5-dien-1-ol(189).

Ethyl 3,5-hexadienoate (172) (0.5g, 3.6 mmol) in anhydrous ether (2ml) was added to a suspension of lithium aluminium hydride (0.27g, 7.1 mmol) in anhydrous ether (10ml). The mixture was heated under reflux for 2h then ethyl acetate was added dropwise to destroy the excess of lithium aluminium hydride. Water was added carefully, with shaking, to tne mixture until a paste adhered to the sides of the flask. Sulphuric acid (1M, 3ml) was added to dissolve the white solid, and the layers were separated. The aqueous layer was extracted with ether (4x30ml). The combined organic layers were washed with

saturated sodium hydrogen carbonate and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the crude residue was distilled to give the alcohols (189) and (189a) in the ratio of 9:1 (combined yield 0.30g, 86%), b.p. 82°C (30mm Hg); δ($CDCl_3$, 90 MHz); 2.32 (2H, q, J 6Hz), 2.25 (1H, Br.S), 3.68 (2H, t, J 6Hz), and 4.85-6.65 (5H, m); (Found m/z 98.0720. Calc. for $C_6H_{10}O$: M, 98.0730); m/z 98, 83, 79 (100%), and 67.

Preparation of the 3,5-Hexadienyl Ester (190) of the Anthracene Cycloadduct Acid (183).

N,N′-Carbonyldiimidazole (0.50g, 3.09 mmol) was dissolved in analar dichloromethane (5ml) in a 3-necked round bottomed flask having a guard tube to exclude moisture. The anthracene cycloadduct acid (183) (0.44g, 1.64mmol) was injected in analar dichloromethane (10ml) into the reagent solution. Carbon dioxide was evolved. The mixture was stirred for 2h. 3,5-Hexadien-1-ol(189) (0.16g, 1.64mmol) in analar dichloromethane (2ml) was treated with n-butyl-lithium (0.071g, 1.58M, 10% mol. equiv. of the alcohol) and the mixture was stirred for 20 min, then was injected into the acid mixture. The reaction mixture was stirred at room temperature overnight then was diluted with analar dichloromethane (30ml). The mixture was washed with aqueous sodium carbonate (0.5M, 20ml) and water (3x30ml), and was dried with Na_2SO_4) and evaporated under reduced pressure with heating. The residue (0.553g) was chromatographed on a silica (HF_{254}) column eluted with analar dichloromethane-light petroleum (b.p.60-80°C) (50:50) to give impure material (0.41g). This was separated on preparative, silica plates developed three times with dichloromethane-light petrolueum (60-80°C) (30:70) to afford the ester (190) (200mg, 35%) (Found: m/z 348.1202. $C_{22}H_{20}O_2S$ requires M, 348.1184): ν_{max}($CHCl_3$) 1735 cm^{-1}; δ($CDCl_3$, 90 MHz) 2.05 (2H, q, J 6Hz, 2′-CH_2), 3.80 (t, J 6Hz,

1'-CH_2), 3.85 (d, J 3Hz, 12-H), 4.65-6.40 (m, vinyl-H), 6.70-7.30 (m, Ar-H).

The foregoing experiment was repeated with a longer reaction time. N,N'-carbonyldi-imidazole (0.40g, 2.47 mmol) was dissolved in analar dichloromethane (5ml). The anthracene cycloadduct acid (183) (0.44g, 1.64 mmol) was injected in analar dichloromethane (10ml) into the reagent solution. The mixture was stirred for 4h. 3,5-Hexadien-1-ol (189) (0.10g, 1.02mmol) in dichloromethane (2ml) was treated with n-butyl-lithium (0.045g, 1.58M) and the mixture was stirred for 30 min then was injected into the acid mixture. The reaction mixture was stirred at room temperature overnight then was worked-up and chromatographed as before to give the product (190) (0.25g, 43.8%). The ^1H n.m.r. data were essentially the same as before.

Preparation of 7-Thia-4-oxabicyclo[4.4.0]dec-9-ene-5-one (191).

The hexadienyl ester (190) of the anthracene cycloadduct (183) (0.26g, 7.60 mmol) was refluxed in distilled toluene (10ml) for 4h. The toluene was evaporated under reduced pressure with heating. The ^1H n.m.r. spectrum of the residue indicated the presence of the expected lactone (19). The mixture was shaken with a small amount of analar chloroform and then was filtered to remove some of the anthracene. The filtrate was then chromatographed on a silica (HF_{254}) column, eluted with cnloroform-light petroleum (1:1) to give the lactone (60mg, 46%) (Found: m/z 170.0408. $C_8H_{10}O_2S$ requires M, 170.0401); ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ(CD_3Cl_3, 90 MHz) 1.7-2.2 (m, 2-CH_2), 3.00 (m, 1-H), 3.15 (m, 8-CH_2), 3.77 (d, J 5.8Hz, 6-H), 4.35 (t, J 5.5 Hz, 3-CH_2), and 5.70 and 6.01 (m, 9- and 10-H).

Preparation of the Cycloadduct (140) of Ethyl Thioxoacetate and Cyclohexa-1,3-Diene.

The Bunte salt (1.11g, 5 mmol) and calcium chloride dihydrate (0.735g, 5mmol) were dissolved in ethanol (20ml). 1,3-Cyclohexadiene (0.417g, 5mmol) was added in benzene (18ml) to the mixture followed by triethylamine (0.505g, 5mmol) in benzene (2ml). The reaction mixture was stirred at room temperature for 3 days then was diluted with chloroform (30ml) and water (30ml), then was acidified with 5% hydrochloric acid until a clear solution had formed. The organic layer was washed with aqueous sodium hydrogen carbonate, brine (10ml), and water (20ml) and was dried ($MgSO_4$) and evaporated under reduced pressure with slight heating to give a crude mixture (0.55g, 53.4%). The product mixture was chromatographed on a silica (HF_{254}) column. Elution with light petroleum chloroform (70:30) gave the endo isomer (140) (0.45g, 43.6%) as a yellow oil. The ^1H n.m.r. data were essentially identical with those reported[4] in literature.

Competition Reactions Between 1-Methoxy-1,3-Cyclonexadiene and 1,3-Cyclohexadiene with Ethyl Thioxoacetate.

1-Methoxy-1,3-cyclohexadiene (5mmol) and 1,3-cyclohexadiene (5mmol) were treated with the Bunte salt (151a) (5mmol), calcium chloride (5mmol) and triethylamine (5mmol) under the usual conditions. After 3 days the mixture was worked-up, as usual, to give a crude mixture (1.05g, 65%) containing the cycloadducts (161) and (162) of methoxycyclohexadiene. The ^1H n.m.r. spectrum of this mixture showed signals for the endo (161) and exo-adduct (162) (ratio 4:1); no signals for the cycloadduct of cyclohexadiene were observed in the regions δ6.29 and δ6.69.

The foregoing experiment was repeated using the methoxy cyclohexadiene

(5mmol) and cyclohexadiene (10mmol). The Bunte salt (1.11g, 5mmol) and calcium chloride dihydrate (0.735g, 5mmol) were dissolved in ethanol (20ml). The dienes were added in benzene (20ml) to the salt mixture. Triethylamine (0.505g, 5mmol) in benzene (2ml) was then added. The reaction mixture was stirred for 4 days then was worked-up as usual to give the cycloadducts (161) and (162) of methoxycyclohexadiene (1.15g, 70%) as a yellow oil. The ^{1}H n.m.r. spectrum showed only signals for the endo (161) and exo-adduct (162) (ratio 4:1).

Competition Reaction Between 1-Methoxy-1,3-Cyclohexadiene and Thebaine with Ethyl Thioxoacetate.

1-Methoxy-1,3-cyclohexadiene (0.161g, 1.46 mmol) and thebaine (0.455g, 1.46 mmol) were treated with the Bunte salt (151a) (0.33g, 1.46 mmol), calcium chloride dihydrate (0.22g, 1.46 mmol) and triethylamine (0.147g, 1.46 mmol) under the usual conditions. After 5 days the mixture was diluted with chloroform (30ml) and water (30ml), then filtered through Celite. The filtrate was evaporated to dryness to give a mixture of the cycloadducts of both dienes (160) and (138) (0.895g) in the ratio ca. 3:2, respectively, as judged by ^{1}H n.m.r. spectroscopy. The cycloadducts were separated on preparative silica plates developed several times with light petroleum-ether (8:3) to give the methoxycyclohexadiene adducts (161) and (162) (0.14g, 36%) and thebaine cycloadduct (142) (0.13g, 20.5%). The ^{1}H n.m.r spectra of each isomer (161) and (162) agreed well with those observed before. The ^{1}H n.m.r. of the thebaine adduct (142) agreed with that reported[56] in the literature.

Competition Reaction Between 1,3-Cyclohexadiene and Methyl Sorbate with Ethyl Thioxoacetate.

1,3-Cyclohexadiene (0.191g, 2.38 mmol) and methyl sorbate

(0.3g, 2.38 mmol) were treated witn the methyl ester Bunte salt (181) (0.49g, 2.38 mmol), calcium chloride dihydrate (0.35g, 2.38 mmol), and trietnylamine (0.24g, 2.38 mmol), under the usual conditions. After 4 days, the mixture was worked-up, as usual, to give a crude mixture (0.4631g) containing the cyclohexadiene cycloadduct (151) and methyl sorbate (182). The ^{1}H n.m.r. spectrum of the mixture showed signals only for the cyclohexadiene adduct (140); no signals for the methyl sorbate cycloadducts (185) and (186) were observed.

Preparation of 1-(4a,9b-Dihydro-8-9b-dimethyl-3-dibenzofuranyl) pyrrolidine (193).

Following the published[72] method, pyrrolidine (0.85ml) was added to a suspension of 4a,9b-dihydro-8,9b-dimethyl-dibenzo-furan-3(4H)-one, Pummerer's ketone[83] (192) (0.50g, 2.3mmol) in methanol (12.5ml), and the mixture was heated on a steam bath for 10 min. The resulting clear yellow solution was allowed to stand at room temperature for 1h. The solvents were evaporated to yield a yellow syrupy residue which was redissolved in benzene and evaporated to dryness to yield the dienamine (193) (0.61g, 98%) as a yellow syrupy. [Found: m/z 267(M, basepeak)]; ν_{max} ($CHCl_3$) 1580 (weak band) and 1650 cm^{-1} (strong band); δ($CDCl_3$, 90 MHz) 1.36 (S, 9b-CH_3), 1.85 (m, 3'- and 4'-CH_2), 2.25 (S, 8-CH_3), 3.2 (m, 2'- and 5'-CH_2), 4.5-6.5 (bs, 4H), and 6.55-7.2 (m, aryl-H).

Preparation of the Cycloadduct (195) of Ethyl Thioxoacetate and 1-(4a,9b-Dihydro-8-9b-dimethyl-3-dibenzofuranyl)pyrrolidine (193).

The Bunte salt (151a) (0.478g, 2.05mmol) and calcium chloride dihydrate (0.32g, 2.05 mmol) were dissolved in ethanol (15ml). The dienamine (193) (0.457g, 1.72 mmol) in benzene (15ml) and triethyl-amine (0.218g, 2.05 mmol) were added to the mixture of salts. The

reaction mixture was stirred at room temperature for 3 days then was diluted with analar chloroform (40ml) and water (30ml). Dilute (5%) hydrochloric acid was added until the calcium sulphite had dissolved and the mixture had become clear. The organic layer was washed successively with aqueous sodium hydrogen carbonate, brine (10ml), and water (20ml), and was then dried ($MgSO_4$) and evaporated. The residue (0.55g) was chromatographed on a silica (HF_{254}) column. Elution with light petroleum-chloroform (1:1) gave a mixture (0.37g) whicn was separated on silica t.l.c. plates developed several times with light petroleum-ether (7:3), to give ethyl 1,2,3,4a,9b-hexahydro-8,9b-dimethyl-3-oxo-4,1-(epithiomethano)dibenzofuran-11-endo-carboxylate (195) (100mg, 18%) (Found: m/z 332.1079. $C_{18}H_{20}O_4S$ requires M, 332.1077; $\nu_{max}(CHCl_3)$ (strong band) 1730 cm^{-1}, $\delta(CDCl_3$, 90 MHz) 1.28 (t, J 7.0Hz, OCH_2CH_3), 1.67 (S, 9b-CH_3) 2.26 (S, 8-CH_3), 1.97-2.57 (m, 2-CH_2), 2.92 (m, 1-H), 3.35 (d, J 4.0Hz, 4-H), 4.11 (m, 11-H), 4.21 (q, J 7Hz), 4.86 (d, J 4.0Hz, 4a-H), and 6.60-6.95 (m, 6-, 7- and 9-H); $\delta(CDCl_3$; 200 MHz) 1.28 (t, J 7.2Hz, OCH_2CH_3), 1.63(S, 9b-CH_3), 1.97 (ddd, J 19.8, 3,3, and 1.3 Hz, 2α-H), 2.26 (S with fine splitting, 8-CH_3), 2.57 (dd, J 19.8 and 3.1Hz, 2β-H), 2.92 (qd, J 3.1 and 0.8Hz, 1-H), 3.35 (d, J 4.0Hz, 4-H), 4.11 (dd, J 2.9 and 1.3 Hz, 11-H), 4.21 (q, J 7.2 Hz, OCH_2CH_3), 4.86 (dd, J 4.0 and 0.7 Hz, 4a-H) 6.61 (dm, J 8.2 and 0.4 Nz, 6-H), 6.86 (dp, J 1.9 and 0.6 Hz, 9-H), and 6.93 (ddq, J 8.2, 1.9 and 0.6 Hz, 7-H).

Preparation of the Cycloadduct Ketone (195) Using 3 mol Equivalents of the Bunte Salt.

The Bunte salt (151a) (0.743g, 3.35 mmol) and calcium chloride dihydrate (0.493g, 3.35 mmol) were dissolved in ethanol (15ml). A mixture of the dienamine (193) (0.299g, 1.12 mmol) and triethylamine (0.339g, 3.35 mmol) was added to the mixture of salts. The reaction

mixture was stirred at room temperature for 4 days then was worked-up and chromatographed as described before to give the ketone (195) (0.12g, 33.4%). The ^1H n.m.r. spectrum was identical with that obtained by using 1 mol equivalent of the Bunte salt.

Hydrolysis of the Ester (195).

1.03M sodium hydroxide (1ml) was added to a solution of the ester (195) (40mg, 0.12 mmol) in tetrahydrofuran (2ml) and the mixture was stirred at room temperature overnight. After 24h the solution was concentrated under reduced pressure with heating. The resulting aqueous solution was washed with ether (5x10ml), then acidified with 5% hydrochloric acid (2ml) and extracted with ether (5x10ml). The ethereal extracts were washed with brine (5ml), dried ($MgSO_4$), and evaporated under reduced pressure with slight heating to give the acid (197) (30mg, 83%) as an amorphous solid (Found: m/z 304.0773. $C_{16}H_{16}O_4S$ requires M, 304.0765): ν_{max} ($CHCl_3$) 1730 cm^{-1} (strong band); δ($CDCl_3$, 90 MHz) 1.65 (s, 9b-CH_3), 2.26 (s, 8-CH_3), 1.80-2.90 (m, 2-CH_2), 2.95 (m, 1-H), 3.40 (d, J 4.0Hz, 4-H), 4.19 (m, 11-H), 4.87 (d, J 4.0Hz, 4a-H), 6.57-7.0 (m, 6-, 7- and 9-H), and 8.0 (bs, CO_2H).

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83. Generously supplied by Dr. R. Weswood, Roussel Laboratories Ltd.