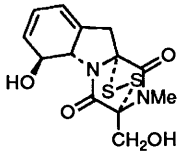
An Investigation of the Retro Diels–Alder Reaction as a Method for the Generation of Diatomic Sulfur

Thomas L. Gilchrist * and Jane E. Wood
Department of Chemistry, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, UK

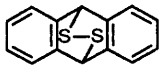
The cyclic disulfides 2,3-dithiabicyclo[2.2.2]oct-5-ene **5**, 1,4-dihydro-2,3-benzodithiin **6** and hexahydro-5,8-epoxy-2,3-benzodithiin **7** have been prepared by oxidation of the corresponding dithiols. Each of these compounds has been subjected to vapour phase pyrolysis in order to determine whether a retro Diels–Alder reaction occurs, leading to the formation of diatomic sulfur (S_2) and a diene. Compounds **5** and **7** both appeared to decompose in this way; in each case the expected diene was detected in the pyrolysate together with sulfur (S_8). Attempts to intercept S_2 and thus to obtain direct evidence for its formation were not successful. The benzodithiin **6** underwent an analogous loss of sulfur on vapour phase pyrolysis, but only as a minor reaction pathway, and this decomposition pathway was not detectable in solution pyrolyses. Solution pyrolysis of **6** in the presence of *N*-phenylmaleimide gave *N*-phenyl-2,3-naphthalimide **21** in low yield. *cis*-Cyclopentene-3,5-dithiol **9** has also been prepared but no evidence could be obtained for the formation of the disulfide **4** on oxidation. Reaction of the dithiol **9** with aldehydes and ketones in the presence of acids led to the formation of adducts (such as **12** and **13** from acetone) which were rapidly interconverted in acidic media.

During the last few years there have been many reports of the generation and trapping of diatomic sulfur (S_2). Steliou, Harpp and their co-workers have pioneered the study of this transient species[1] but several other research groups have produced evidence for S_2 as reaction intermediate.[2,3] We were interested in using S_2 as a dienophile in reactions with cyclic 1,3-dienes which, we hoped, would allow us to produce analogues of biologically active cyclic disulfides such as gliotoxin **1**, although recent work by Steliou *et al.* makes it doubtful whether cyclic dienes do, in general, give simple Diels–Alder adducts with S_2.[1d]

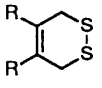
Among the methods reported for the generation of S_2, one of the most direct is that based on the retro Diels–Alder reaction of the dihydroanthracene species **2**. Ando and co-workers have claimed that this compound can be generated in solution but not isolated, S_2 and anthracene being produced at or below 55 °C.[3d] On this basis, the retro Diels–Alder reaction to give S_2 and a diene must be energetically favourable and it might therefore be possible to design a somewhat more stable S_2 precursor which would undergo the retro Diels–Alder reaction on moderate heating.



1



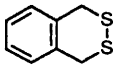
2



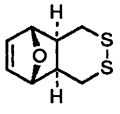
3

4

5



6

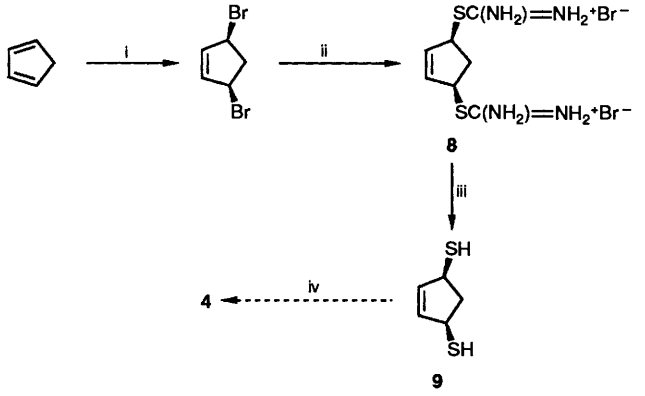


7

One of the apparent inconsistencies in the literature is that, whereas compound **2** is reported to undergo the retro Diels–Alder reaction very easily, there are several other compounds having the correct skeletal arrangement for the reaction but which survive at much higher temperatures. Several monocyclic 3,6-dihydro-1,2-dithiins **3** have been prepared at temperatures up to 130 °C.[1,4] Although these compounds show a tendency to polymerise there is no evidence that they undergo the retro Diels–Alder reaction at this temperature: indeed the Diels-Alder addition of S_2 is an important method of making them.[1] (There is, however, a literature example of the retro Diels–Alder reaction of a monocyclic 3,6-dihydro-1,2-dithiin-1-oxide.[5]) The retro Diels–Alder reaction of compound **2** must be facilitated by the regeneration of the aromatic anthracene ring system, but literature precedents indicate that formal adducts of nonaromatic cyclic dienes such as cyclopentadiene also undergo reverse Diels–Alder reactions on heating.[6] The results reported in this paper are based on an initial decision to prepare compounds which are the formal Diels–Alder adducts of cyclic dienes, and which we hoped would be intermediate in reactivity between **2** and **3**. The first of these target structures was the bridged disulfide **4**, which is the formal Diels–Alder adduct of S_2 and cyclopentadiene. The second was the formal cyclohexadiene adduct **5**, a compound which has previously been isolated by Steliou,[1d] Harpp[1c] and their co-workers. The results which we obtained with these compounds led us on to study the known benzodithiin **6** and to prepare the bridged disulfide **7** as a potential source of S_2. We have also attempted unsuccessfully to repeat the preparation of the dihydroanthracene **2**.

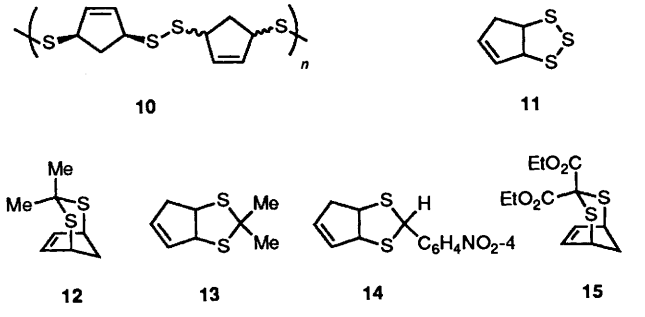
Attempted Synthesis of the Disulfide **4**.—The route to disulfide **4** is summarised in Scheme 1. The first step was the addition of bromine to cyclopentadiene in pentane at low temperature (−20 °C) which, as Winstein and his co-workers showed,[7] gives predominantly *cis*-3,5-dibromocyclopentene. This was treated with thiourea in ethanol to give the dibromide **8** which crystallised as a single isomer. The salt was then hydrolysed to the dithiol **9**. This thiol, which was isolated as an air stable oil, was identified as the *cis* isomer on the basis of its reactions with carbonyl compounds described below.

The oxidation of the dithiol **9** was carried out using iodine,

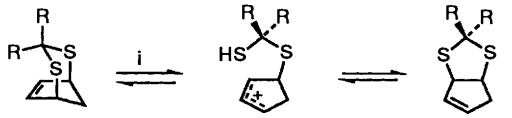


Scheme 1 *Reagents:* i, Br_2, pentane, −20 °C; ii, $(H_2N)_2C{=}S$; iii, NaOH aq. then dil. HCl; iv, MnO_2, −20 °C

iron(III) chloride, lead(IV) acetate and manganese(IV) oxide. Reactions with the first three of these oxidants led to the formation of a solid with a poorly resolved NMR spectrum which may have been the linear polymer **10** (as a mixture of stereoisomers). Manganese(IV) oxide was used as the oxidant in conditions similar to those described by Hayashi and co-workers for the formation of a prostaglandin disulfide from the dithiol, namely, reaction at −20 °C under argon.[8] The reaction mixture was examined by NMR spectroscopy at low temperature but again the spectrum was poorly resolved and changed over a period of a few hours. An oil was isolated by flash chromatography but this also had a poorly resolved NMR spectrum. The oil was analysed by mass spectometry under electron impact, which produced a spectrum with a major ion at *m/z* 162. This corresponds to an adduct of cyclopentadiene with S_3 and we considered the possibility that the compound was the trisulfide **11** reported by Steliou *et al.* as the ultimate product of the reaction of cyclopentadiene with diatomic sulfur.[1d] The NMR spectrum reported for compound **11** did not correspond to any of those recorded by us, however; in particular, there was an absence of signals in the region δ 4.5–5.5 in all the spectra which we recorded. The spectra obtained by us, although variable, were all more consistent with a 3,5-disubstituted cyclopentene. To test the possibility that the oil might have contained the disulfide **4** as a component, it was heated in norbornadiene which is known to be an S_2 acceptor. No sulfur transfer product was obtained with norbornadiene, and there is therefore no evidence that the disulfide **4** is formed by oxidation of the thiol **9**.



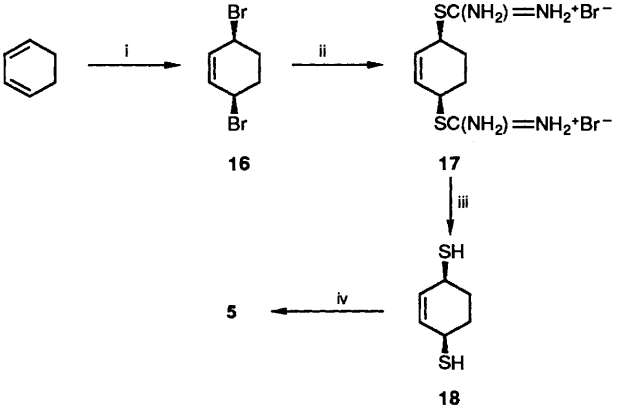
Attempts were also made to synthesise **4** using the indirect method of conversion of dithiols into cyclic disulfides originally devised by Kishi.[9] In this procedure the *cis* dithiol is converted into a cyclic dithioacetal by reaction with anisaldehyde and the dithioacetal is then cleaved oxidatively. The dithiol **9** reacted readily with a range of aldehydes and ketones under acid catalysis but none of the reactions gave a single product. From GLC and NMR analysis it became clear that the product mixture contained dithioacetals of two types. The product derived from acetone was shown by NMR spectroscopy to consist of a mixture of the dithioacetals **12** and **13**. The ratio of the two isomers varied randomly. With 4-nitrobenzaldehyde the crude product was a more complex mixture because two diastereoisomeric forms of each type of structure are possible. A solid which was isolated from the mixture by chromatography was identified as one of the 3,4-disubstituted cyclopentenes **14** from its NMR spectrum. We could not identify conditions in which the 3,5-isomers were the major components with these or other dithioacetals prepared in the presence of an acid catalyst. Apparently the isomers are rapidly interconverted in acidic



Scheme 2 *Reagents:* i, H^+ or BF_3

media (Scheme 2). Only one adduct was prepared which was isolated exclusively as the 3,5-isomer. Diethyl ketomalonate was sufficiently reactive to form a dithioacetal with the dithiol **9** in the absence of an acid catalyst; the reaction gave exclusively the dithioacetal **15**. However, because of the rapid isomerisation observed with aldehydes, this route to the disulfide **4** was not pursued.

Preparation and Pyrolysis of the Disulfide **5**.—Compound **5** has previously been prepared in low yield by the addition of S_2 to cyclohexa-1,3-diene.[1c,d] We have prepared the disulfide on a larger scale by a route (shown in Scheme 3) which is directly



Scheme 3 *Reagents:* i, Br_2, pentane, −20 °C; ii, $(H_2N)_2C{=}S$; iii, NaOH aq. then dilute HCl; iv, MnO_2, −20 °C

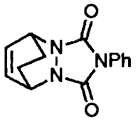
analogous to that used for the attempted preparation of the disulfide **4**. Like cyclopentadiene, cyclohexa-1,3-diene undergoes *cis*-1,4-addition of bromine at low temperature.[10] The dibromocyclohexene **16** prepared in this way reacted with thiourea to give the salt **17**, which was hydrolysed to the dithiol **18**. The dithiol, a yellow oil, was fully characterised. It was oxidised by manganese dioxide below 0 °C to the disulfide **5**. We found that, as reported by Steliou *et al.*,[1d] the disulfide was volatile and could be purified by distillation. It was isolated as a yellow oil which was characterised by NMR spectroscopy and by mass spectrometry but it proved impossible to store the compound because it rapidly decomposed to an amorphous colourless solid.

A freshly prepared sample of the disulfide **5** was pyrolysed in the vapour phase. The compound was heated *in vacuo* and the vapour was passed through a silica tube heated at 650 °C. The pyrolysate was then condensed on a surface cooled by liquid nitrogen. The only products detected were sulfur (S_8) and

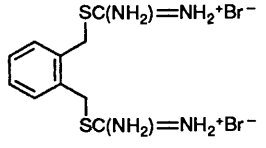
cyclohexa-1,3-diene. Cyclohexadiene was identified by NMR spectroscopy and by trapping with *N*-phenyltriazolinedione as the known[11] cycloadduct **19**, which was isolated in 21% yield (based on the mass of disulfide **5** which had pyrolysed).

It is surprising that the disulfide **5** decomposes thermally only by this route. Attractive alternative modes of pyrolytic breakdown can be envisaged involving S–S bond cleavage, loss of H_2S and aromatisation but there was no evidence for this type of decomposition. The observed mode of breakdown to give cyclohexadiene is most simply interpreted as a retro Diels–Alder reaction, although direct evidence for the generation of S_2 is lacking at present. An attempt was made to intercept S_2 by coating the cold trap with 2,3-dimethylbutadiene but no S_2 adduct was formed.

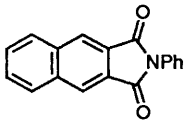
Pyrolysis of the Benzodithiin **6**.—The observed mode of thermal breakdown of the dithiol **5** led us to seek more stable precursors of a similar type. 1,4-Dihydro-2,3-benzodithiin **6** was selected as it was reported as a stable crystalline solid. It was prepared by a method analogous to that of Milligan and Swan[12] but with the isothiouronium salt **20** as an intermediate



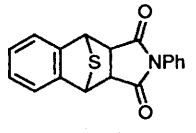
19



20



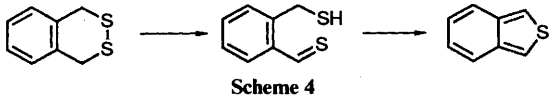
21



22

in place of the Bunte salt. Flash pyrolysis of the compound at 650 °C and 0.1 mmHg gave a mixture containing starting material, elemental sulfur, and several other components. The presence of benzocyclobutane was established by GLC–mass spectrometry but the yield was low (< 10%). Hydrogen sulfide was also detected; the formation of benzocyclobutane (presumably by way of *o*-xylylene) is not the major reaction.

Pyrolyses of compound **6** were also attempted in solution. After the compound had been heated in xylene for 24 h in the presence of *N*-phenylmaleimide a product was isolated in low yield and was identified as the imide **21** by comparison with an authentic specimen. The source of this adduct is uncertain. It could be derived from benzo[*c*]thiophene which in turn is derived from the benzodithiin **6** by loss of H_2S (Scheme 4); one

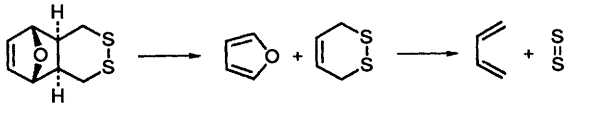


Scheme 4

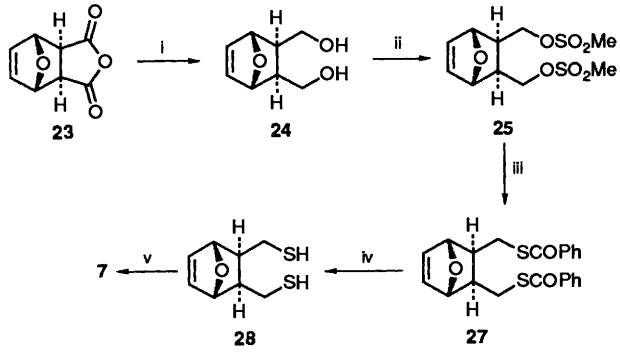
earlier example of an extrusion of H_2S from a benzodithiin has been reported.[13] On the other hand, the reaction of benzo[*c*]thiophene with *N*-phenylmaleimide has previously been reported to give the Diels–Alder adduct **22**.[14]

Thus the benzodithiin **6** does not appear to be a useful source of S_2 either in solution or in the vapour phase, although retro Diels–Alder decomposition may be a minor pathway in the vapour phase.

Preparation and Pyrolysis of the Disulfide **7**.—The easy polymerisation of simple 3,6-dihydro-1,2-dithiins makes them unsuitable as potential S_2 precursors. In an attempt to circumvent this problem we have prepared the disulfide **7**. The choice of structure **7** as a target was made on the basis that removal of the double bond from the six-membered ring might make the compound more stable, and that **7** could still act as a suitable S_2 source by a 'double' retro Diels–Alder reaction as shown in Scheme 5.

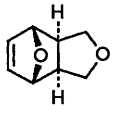


Scheme 5

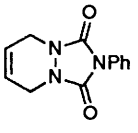


Scheme 6 *Reagents:* i, $LiAlH_4$; ii, $MeSO_2Cl$, pyridine; iii, PhCOSNa; iv, $LiAlH_4$; v, MnO_2, −20 °C

The route to disulfide **7** is outlined in Scheme 6; it involves a series of standard functional group transformations starting from the furan–maleic anhydride adduct **23**.[15] This anhydride was reduced by lithium aluminium hydride to the known[15] diol **24**. Attempts were made to convert the diol into its ditosylate, and also directly into the dichloride by the method of Nicolaou and coworkers,[16] but these resulted in the formation of mixtures. The dimesylate **25** was then prepared, although under a variety of conditions the ether **26** was also formed as a by-



26



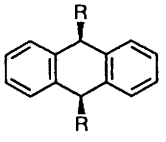
29

product and had to be removed by chromatography. The mesylate was converted into the thioester **27** which in turn was cleaved to the dithiol **28** by reaction with lithium aluminium hydride.[17] The dithiol was obtained as a yellow oil which became semicrystalline when dried *in vacuo* but which was not stable enough to survive further attempts at purification. Its structure was established from its NMR spectrum, which showed the expected triplet, equivalent to two hydrogens, for the SH hydrogens at δ 1.45, and by high resolution mass spectrometry. Finally the thiol was oxidised to the disulfide **7** by manganese dioxide. The disulfide was obtained as a yellow oil and was characterised by mass spectrometry and by NMR spectroscopy. Unfortunately the compound proved to be hardly more stable than the dithiin **5**: it could be purified by rapid chromatography but it polymerised in the condensed phase within 24 h, even when stored below 0 °C. Thus the main objective of carrying out this preparation, to obtain a stable, storable S_2 precursor, was not achieved.

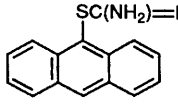
Nevertheless the postulated mode of unimolecular thermal decomposition shown in Scheme 5 has some experimental support. The disulfide **7** was pyrolysed in the vapour phase and the pyrolysate was intercepted on a condenser cooled by liquid nitrogen. The presence of butadiene in the pyrolysate was established by its reaction with *N*-phenyltriazolinedione. This gave (29%)

the adduct **29** which was identified by comparison with an authentic specimen.[18] Sulfur was also detected as a product. The fragmentation shown in Scheme 5 can account for presence of butadiene and sulfur, but again, there is no direct evidence that S_2 is being generated. It is worth noting that the electron impact mass spectrum of the disulfide **7** (M 186) shows major peaks at mass 118 (equivalent to the loss of furan) and at 54 ($C_4H_6^+$).

Attempted Preparation of Disulfide **2**.—We report briefly here on failed attempts to prepare the dihydroanthracene **2**. Addition of bromine to anthracene at low temperature gave 9,10-dibromo-9,10-dihydroanthracene **30**.[19] This proved to be too unstable to characterise by NMR spectroscopy but reaction with pyridine[20] gave a solid dipyridinium salt. The NMR spectrum of the salt in D_2O showed it to be a single isomer which showed a singlet for 9-H and 10-H at δ 7.76. We have assigned this as the *cis* isomer **31** by analogy with the structures of salts **8** and **17**. (Although the problem of the stereochemistry of 9,10-dibromo-9,10-dihydroanthracene was addressed by Barnett, Cook and Matthews[21] we are not aware that the structure has ever been firmly established as *cis* or *trans*.) Many attempts were made to prepare the isothiouronium salt **32** from the dibromide **30**. Because of the low solubility of the dibromide in ethanol this solvent proved to be unsuitable; all attempts to carry out the reaction in ethanol led instead to the formation of 9-bromoanthracene. The problem was partly solved by dissolving the dibromide in a mixture of acetonitrile and xylene and rapidly stirring the solution below 0 °C while thiourea was



30; R = Br
31; R = $C_5H_5N^+$ Br^-
32; R = $SC(NH_2)=NH_2^+Br^-$



33

added. This allowed a sample of the salt **32** to be isolated and its NMR spectrum to be obtained. The spectrum showed a singlet (2 H) at δ 6.90 for H-9 and H-10 and two symmetrical multiplets at δ 7.45–7.52 and 7.65–7.75 (each 4 H) for the aromatic hydrogens. The salt rapidly decomposed to give the elimination product **33** and this was also the major product of the attempted hydrolysis of the salt in ethanol.

Conclusions.—The major finding from this work is that 3,6-dihydrodithiins can extrude both sulfur atoms on pyrolysis. The retro Diels–Alder fragmentation to give S_2 and a diene, analogous to that proposed by Ando *et al.* for the dihydroanthracene **2**, provides a rationale for these observations. The reaction may provide a means of generating S_2 in the vapour phase but a precursor which will allow the reaction to be used as a source of S_2 in solution has not yet been found.

Experimental

^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200 MHz, on a Bruker WM250 instrument operating at 250 MHz or on a Bruker AMX400 instrument operating at 400 MHz. Signals are singlets where no multiplicity is shown. Deuteriochloroform was used as the solvent except where indicated otherwise. *J* Values are given in Hz and signals are singlets unless indicated otherwise. Mass spectra were recorded under electron impact on a VG Micromass 7070E instrument. Microanalyses were performed in the microanalytical laboratory at Liverpool University. M.p.s were obtained on a Reichert hot-stage apparatus and are uncorrected. Flash column chromatography was performed using Merck 9385 silica as the stationary phase.

cis-*Cyclopentene*-3,5-*dithiol* **9**.—(*a*) *cis*-3,5-Dibromocyclopentene was obtained as a crystalline solid by the method of Winstein *et al.*[7] The solid (29.7 g, 0.13 mol) was stored at −78 °C and portions were added slowly to a solution of thiourea (20.0 g, 0.26 mol) in ethanol (300 cm^3) which was heated under reflux. After all the solid had been added, the reaction mixture was maintained at reflux temperature. It became clear, then after a few minutes, a colourless precipitate appeared. The solid was filtered off, washed with hot ethanol and dried to give cis-*cyclopentene*-3,5-*bisisothiouronium bromide* **8** (21.6 g, 65%), m.p. 196 °C (Found: C, 21.85; H, 3.65; N, 15.0. $C_7H_{14}Br_2N_4S_2$ requires C, 22.2; H, 3.7; N, 14.8%); δ[200 MHz; $(CD_3)_2CO$] 2.26 (1 H, br d, *J* 15.7, 4-H), 3.38 (1 H, dt, *J* 15.7 and 7.4, 4-H), 4.93 (2 H, d, *J* 7.4, 3-H and 5-H) and 6.17 (2 H, 1-H and 2-H).

(*b*) The salt **8** (1.00 g, 2.65 mmol) was dissolved in 10% aq. sodium hydroxide (25 cm^3) and the solution was kept at 20 °C for 0.5 h. It was then cooled in ice, made acidic with dilute HCl, and extracted with dichloromethane (3 × 50 cm^3). The organic extracts were dried ($MgSO_4$) and the residue was purified by column chromatography using a gradient eluent of ethyl acetate (0–10%) in cyclohexane. This gave the *title compound* **9** (0.27 g, 78%) as a yellow oil with a pungent smell resembling roast beef (Found: C, 45.5; H, 6.1%; M^+, 132.0067. $C_5H_8S_2$ requires C, 45.45; H, 6.1%; *M*, 132.0070); δ(200 MHz) 1.97 (2 H, d, *J* 8.4, SH), 2.05 (1 H, dt *J* 14.6 and 3.1, 4-H), 2.98 (1 H, dt, *J* 14.6 and 8.1, 4-H), 3.88 (2 H, ddd, *J* 8.4, 8.1 and 3.1, 3-H and 5-H) and 5.81 (2 H, 1-H and 2-H).

Oxidation of the Dithiol **9**.—The following is typical of several experiments. The dithiol **9** (100 mg) in $CDCl_3$ (1.0 cm^3) was stirred at −30 °C under argon with freshly prepared manganese(IV) oxide (0.5 g) until the starting material had been consumed (0.5 h). The reaction mixture was rapidly filtered and the filtrate was transferred to an NMR tube; δ(250 MHz; −30 °C) 2.14–2.18 (*ca.* 3 H, m, possibly including H_2O signal), 2.80–3.05 (*ca.* 1 H, m), 3.98–4.10 (*ca.* 2 H, m) and 5.80–6.00 (*ca.* 2 H, m). The sample was warmed to +30 °C and the spectrum, recorded at intervals, showed no significant change. Flash chromatography (ethyl acetate–cyclohexane, 1:10) gave an oil (0.3 g) which showed a similar NMR spectrum to that above, but with all signals broader, and had *m/z* 194 ($C_5H_6S_4^+$, 9%), 162 ($C_5H_6S_3^+$, 31%), 130 ($C_5H_6S_2^+$, 89%), 98 ($C_5H_6S^+$, 57%), 97 ($C_5H_5S^+$, 66%) and 66 ($C_5H_6^+$, base). For other samples the ratio of peaks at 162 and 130 was different, that at 162 being the major peak.

3,3-*Dimethyl*-2,4-*dithiabicyclo*[3.2.1]*oct*-6-*ene* **12** *and* 4,6a-*dihydro*-2,2-*dimethyl*-3a*H*-*cyclopenta*-1,3-*dithiole* **13**.—To a solution of acetone (0.46 g, 8.0 mmol) in dichloromethane (30 cm^3) at 0 °C was added boron trifluoride etherate (1.13 g, 8.0 mmol); the dithiol **9** (1.04 g, 80 mmol) in dichloromethane (10 cm^3) was then added slowly during 1 h. The reaction mixture was stirred overnight at room temperature, 10% aqueous sodium hydrogen carbonate (70 cm^3) was added, and the mixture stirred for a further 3 h. The organic layer was then separated, washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue, a brown oil, was subjected to flash chromatography (ethyl acetate–cyclohexane, 1:10). This gave, as a viscous oil, the title compounds (0.77 g, 57%) as a mixture; ratio of **12**–**13** by NMR and GLC 1:8, δ(200 MHz) (for **12**) (1.40, CH_3), 1.80 (CH_3), 2.40 (d, 8-H), 3.00 (dt, 8-H), 3.75 (br d, 1-H and 5-H) and 6.15 (6-H and 7-H); (for **13**) 1.77 (CH_3), 1.80 (CH_3), 2.70 (br d, 4-H), 3.00 (dd, 4-H), 4.60 (approx. dt, 3a-H), 5.00 (br d, 6a-H) and 5.75 (5-H and 6-H).

The reaction was also carried out with dry HCl as catalyst, at room temperature and below 0 °C. The ratio of the isomers varied between 1:8 (at room temperature) and 1:1 (rapid analysis following reaction at −35 °C).

4,6a-*Dihydro*-2-(4-*nitrophenyl*)-3a*H*-*cyclopenta*-1,3-*dithiole* **14**.—The reaction was carried out as for the preparation of dithioacetals **12** and **13** described above, but with 4-nitrobenzaldehyde (1.20 g, 8.0 mmol) in place of acetone. Flash chromatography gave the *title compound* **14** as brown crystals m.p. 120–125 °C (Found: C, 54.4; H, 4.5; N, 5.3%; M^+, 265.0231. $C_{12}H_{11}NO_2S_2$ requires C, 54.3; H, 4.15; N, 5.0%; *M*, 265.0231); δ(250 MHz) 2.76 (1 H, br d, *J* 17.5, 8-H), 3.03 (1 H, dd showing further splitting, *J* 17.5 and 7.3, 8-H), 4.67 (1 H, approx. dt, *J* 2.5 and 7.3, 3a-H), 5.05 (1 H, dd showing further splitting, *J* 6.6 and 1.8, 6a-H), 5.65–5.70 (1 H, m, 6-H), 5.90–5.94 (1 H, m, 5-H), 7.26 (1 H, 2-H), 7.72 (2 H, d, *J* 8.7) and 8.17 (2 H, d, *J* 8.7).

A sample of the reaction mixture analysed by NMR spectroscopy before workup showed the presence of other isomers; *e.g.*, signals attributable to a 2,4-dithiabicyclo[3.2.1]oct-6-ene at δ 3.87 (d, *J* 5.4, 1-H and 5-H) and 6.18 (6-H and 7-H).

Diethyl 2,4-*Dithiabicyclo*[3.2.1]*oct*-6-*ene*-3,3-*dicarboxylate* **15**.—To a solution of the dithiol **9** (0.70 g, 5.2 mmol) in dichloromethane (50 cm^3) at 0 °C was added over a period of 1 h diethyl ketomalonate (0.92 g, 5.22 mmol) in dichloromethane (10 cm^3). The solution was kept at room temp. for 12 h, the solvent was distilled off, and the residue was subjected to flash chromatography (ethyl acetate–cyclohexane, 1:10). This gave the *title compound* **15** as a yellow oil (1.14 g, 76%) (Found: C, 50.0; H, 5.55. $C_{12}H_{16}O_4S_2$ requires C, 50.0; H, 5.55%); ν_{max}(film)/cm^{-1} 1740; δ(200 MHz) 1.30 (3 H, t), 1.32 (3 H, t), 2.10 (1 H, dt, *J* 15.3 and 4.4, 8-H), 2.92 (1 H, dt, *J* 15.3 and 8.4, 8-H), 4.12 (2 H, dd, *J* 8.4 and 4.4, 1-H and 5-H), 4.31 (2 H, q), 4.33 (2 H, q) and 5.80 (2 H, 6-H and 7-H); *m/z* 288 (M).

2,3-*Dithiabicyclo*[2.2.2]*oct*-5-*ene* **5**.—(*a*) *cis*-3,6-Dibromocyclohexene **16** was prepared[10] by the addition of bromine to cyclohexa-1,3-diene in pentane at −20 °C followed by crystallisation at −78 °C and it was isolated (61%) as a colourless crystalline solid, unstable at room temperature; δ(200 MHz) 2.08–2.40 (4 H, m), 4.76 (2 H, t) and 5.96 (2 H). This solid (9.0 g, 0.037 mol) was added in portions to a solution of thiourea (5.70 g, 0.075 mol) in ethanol (200 cm^3) which was being heated under reflux. The heating was continued after all compound **16** had been added until a precipitate appeared from the hot reaction mixture. The solid was filtered off, washed with hot ethanol (3 × 50 cm^3) and dried; this was characterised as *cyclohexene*-3,6-*bisisothiouronium dibromide* **17** (12.0 g, 82%), m.p. 218–220 °C (Found: C, 24.6; H, 4.1; N, 14.4. $C_8H_{16}Br_2N_4S_2$ requires C, 24.5; H, 4.1; N, 14.3%); δ[200 MHz; $(CD_3)_2SO$] 1.70–1.89 (2 H, m), 2.05–2.28 (2 H, m), 4.58–4.70 (2 H, poorly resolved t), 6.00 (2 H) and 9.20 (8 H, br).

(*b*) The salt **17** (1.50 g, 3.82 mmol) was dissolved in 10% aqueous sodium hydroxide (25 cm^3) at room temperature. After 0.5 h, the solution was cooled in ice and acidified with dil. HCl. The organic product was extracted with dichloromethane (3 × 50 cm^3), the extracts were dried ($MgSO_4$) and the solvent was removed. Flash chromatography using gradient elution (cyclohexane with ethyl acetate 0–20%) gave cis-*cyclohexene*-3,6-*dithiol* **18** (0.46 g, 82%) as a yellow oil with a pungent odour (Found: C, 49.2; H, 6.8. $C_6H_{10}S_2$ requires C, 49.3; H, 6.8%); δ(200 MHz) 1.67 (2 H, d, *J* 8.4, SH), 1.75–1.90 (2 H, m), 1.95–2.10 (2 H, m), 3.36–3.50 (2 H, poorly resolved dt) and 5.66 (2 H).

(*c*) A solution of the dithiol **18** (0.28 g, 1.91 mmol) in dry dichloromethane (25 cm^3) was added slowly to a suspension of freshly prepared manganese(IV) oxide (0.66 g, 7.64 mmol) in dry dichloromethane (20 cm^3) under argon at −20 °C. The mixture was stirred at this temperature for 4 h. The mixture was then filtered and the filtrate was evaporated to leave a viscous yellow oil (0.19 g, 68%). The oil was found to decompose to an amorphous colourless solid, and this decomposition was accelerated when flash chromatography was attempted. Distillation *in vacuo* gave a specimen of the *title compound* **5** as a yellow oil (Steliou *et al.*[14] report the pure compound as a crystalline solid; no m.p. given) (Found: M^+, 144.005. $C_6H_8S_2$ requires *M*, 144.001); δ(200 MHz) 1.83–2.28 (4 H, m), 3.50 (2 H, br) and 5.88 (2 H).

Vapour Phase Pyrolysis of the Disulfide **5**.—A freshly distilled specimen of the disulfide **5** (0.200 g) was put in a flask at room temperature which was attached to a silica tube and a condenser system. The silica tube was heated to 650 °C and the pressure was reduced to 0.1 mmHg, so that the disulfide slowly vapourised and the vapour passed through the hot tube. The condenser was cooled by liquid nitrogen. After 4 h the pyrolysis was stopped; the mass of disulfide which had pyrolysed was 0.080 g. The condenser was washed with $CDCl_3$ (leaving an insoluble residue of sulfur) and an NMR spectrum of the solution was taken. This showed only the signals of cyclohexa-1,3-diene: δ(200 MHz) 2.18 (4 H) and 5.65–5.98 (4 H, m). To the solution used for the NMR determination was then added dropwise a solution of *N*-phenyltriazolinedione (50 mg) in acetone (5 cm^3) until the solution retained a pink colouration, showing that the dienophile was in excess. Flash chromatography gave [with ethyl acetate (0–10%) in cyclohexane] the cycloadduct **19** (0.030 g, 21% based on the mass of disulphide **5** which had pyrolysed), m.p. 171–174 °C (lit.,[11] 172.5–174.5 °C), which was identified by comparison with an authentic specimen.

1,4-*Dihydro*-2,3-*benzodithiin* **6**.—(*a*) 1,2-Bisbromomethylbenzene (5.0 g, 0.018 mol) was added slowly to a solution of thiourea (2.86 g, 0.038 mol) in ethanol (200 cm^3) which was heated under reflux. Heating was continued until a precipitate appeared. The precipitate was filtered off and was washed with hot ethanol (3 × 50 cm^3) and dried to give *benzene*-1,2-*bismethaneisothiouronium dibromide* **20** (7.43 g, 94%), m.p. 234–236 °C (Found: C, 28.85; H, 3.9; N, 13.5. $C_{10}H_{16}Br_2N_4S_2$ requires C, 28.8; H, 3.8; N, 13.45%); δ[200 MHz, $(CD_3)_2SO$] 4.62 (4 H, 7.30–7.50 (4 H, m) and 9.20 (8 H, br).

(*b*) The salt **20** (5.0 g, 0.012 mol) was dissolved in 10% aqueous sodium hydroxide (50 cm^3). After 0.5 h the solution was cooled in ice and acidified (dilute HCl). The organic product was extracted with dichloromethane. The solution was dried ($MgSO_4$) and the solvent was removed. The residue was purified by flash chromatography [ethyl acetate (0–10%) in cyclohexane] to give benzene-1,2-bismethanethiol (1.16 g, 57%) as a colourless oil (Found: C, 56.4; H, 5.7. Calc. for $C_8H_{10}S_2$: C, 56.5; H, 5.9%); δ(200 MHz) 1.80 (2 H), 3.80 (4 H) and 7.05–7.33 (4 H, m).

(*c*) The dithiol (2.0 g, 0.012 mol) was added slowly to a suspension of manganese(IV) oxide (4.17 g, 0.048 mol) in dry dichloromethane (20 cm^3) under argon at −20 °C. The mixture was stirred for 18 h at this temperature then filtered. The filtrate was evaporated to leave a solid. Flash chromatography [ethyl acetate (0–10%) in cyclohexane] gave the title compound **6** (1.60 g, 81%), m.p. 77–79 °C (lit.,[12] 77–78 °C); δ(200 MHz) 4.20 (2 H) and 7.02–7.16 (4 H, m).

Pyrolysis of Disulfide **6**.—(*a*) *In the vapour phase.* The disulfide **6** (200 mg) was pyrolysed at 650 °C and 0.1 mmHg as described above for compound **5**. In contrast to the above, the pyrolysate from **6** smelled strongly of hydrogen sulfide. Sulfur and benzocyclobutane were detected qualitatively in the pyrolysate, the latter by GLC and MS comparison with an authentic speciment, but NMR analysis was inconclusive.

(*b*) *In solution.* The disulphide **6** (200 mg) was heated in decalin at 196 °C for 48 h with *N*-phenylmaleimide (820 mg). The solvent was removed and the residue was subjected to flash chromatography (ethyl acetate). This gave *N*-phenylnaphthalene-2,3-dicarboximide **21** (10 mg, 3%) m.p. 279–280 °C (lit.,[22] 279–280 °C) which was identified by comparison with an independently synthesised[22] specimen.

1,4,4aα,5α,8α,8aα-*Hexahydro*-5,8-*epoxy*-2,3-*benzodithiin* **7**.—(*a*) The anhydride **23** was prepared (91%) from furan (13.62 g, 0.20 mol) and maleic anhydride (19.62 g, 0.20 mol) in ether during 1 week.[15] This anhydride (20.0 g, 0.12 mol) was reduced by lithium aluminium hydride in tetrahydrofuran to give the diol **24**[15] (13.15 g, 70%) as a viscous oil; δ(200 MHz) 1.90–2.02 (2 H, m), 3.70–3.87 (4 H, m), 3.90 (2 H, br), 4.67 (2 H) and 6.33 (2 H).

(*b*) Methanesulfonyl chloride (6.16 g, 0.053 mol) was added dropwise during 0.5 h at 0 °C to a vigorously stirred solution of the diol **24** (4.0 g, 0.025 mol) in dry pyridine (100 cm^3). The reaction mixture was then allowed to stand at room temperature for 12 h. Sufficient water was added to dissolve the precipitated pyridine hydrochloride then the solution was poured into cold water. The insoluble oil was separated and washed several times with water. It was then diluted with dichloromethane (200 cm^3) and the organic solution was washed with dilute hydrochloric acid and water. It was dried ($MgSO_4$) and evaporated to leave an oil. Flash chromatography [gradient elution; ethyl acetate (0–50%) in cyclohexane] gave 2,3-*bis*(*methylsulfonyloxymethyl*)-7-*oxabicyclo*[2.2.1]*hept*-5-*ene* **25** (4.8 g, 60%), m.p. 128–130 °C (Found: C, 38.6; H, 5.1. $C_{10}H_{16}O_7S_2$ requires C, 38.45; H, 5.2%); δ(400 MHz) 2.20 (2 H, approx. tt, *J* 8.1 and 5.3, 2-H and 3-H), 4.20 (2 H, approx. t, *J* 9.8, one H of CH_2OMs), 4.37 (2 H, dd, *J* 9.8 and 5.3, one H of CH_2OMs), 4.90 (2 H, 1-H and 4-H) and 6.43 (2 H, 5-H and 6-H).

A second product isolated from the column was 1,3,3a,4,7,7a-*hexahydro*-4,7-*epoxyisobenzofuran* **26** (0.35 g, 10%) as a thermally unstable solid, m.p. 33–35 °C (Found: C, 69.3; H, 7.3. $C_8H_{10}O_2$ requires C, 69.6; H, 7.2%); δ(200 MHz) 2.44–2.54 (2 H, m), 3.59 (2 H, dd, *J* 8.8 and 4.9), 3.90–3.96 (2 H, m), 4.75 (2 H) and 6.41 (2 H); *m*/*z* (chemical ionisation) 156 ($M + NH_4^+$) and 139 ($M + H^+$).

(*c*) A solution of the diester **25** (4.00 g, 0.013 mol) and sodium thiobenzoate (4.28 g, 0.026 mol) in dimethylformamide (50 cm^3) was heated at 40 °C for 12 h. It was cooled and poured into a mixture of dichloromethane (200 cm^3), saturated brine (100 cm^3) and saturated aqueous sodium hydrogen carbonate (100 cm^3). The layers were separated, the aqueous layer was extracted with dichloromethane (2 × 50 cm^3) and the combined organic extracts were dried (Na_2SO_4) and evaporated to dryness. The product was isolated by flash chromatography [gradient elution, ethyl acetate (0–50%) in cyclohexane]. This gave 2,3-*bis*(*benzoylthiomethyl*)-7-*oxabicyclo*[2.2.1]*hept*-5-*ene* **27** (4.06 g, 80%), m.p. 123–125 °C (Found: C, 66.7; H, 5.1. $C_{22}H_{20}O_3S_2$ requires C, 66.6; H, 5.1%); δ(400 MHz) 1.98–2.03 (2 H, m, 2-H and 3-H), 3.09 (2 H, dd, *J* 13.3 and 10.5), 3.52 (2 H, dd, *J* 13.3 and 4.4), 4.84 (2 H), 6.35 (2 H), 7.45–7.49 (2 H, m), 7.57–7.60 (1 H, m) and 8.00 (1 H, dd, *J* 8.3 and 1.3); *m*/*z* 396 (M).

(*d*) To a suspension of lithium aluminium hydride (0.38 g, 10.0 mmol) in tetrahydrofuran (20 cm^3) was added dropwise at 0 °C a solution of the diester **27** (1.00 g, 2.52 mmol) in tetrahydrofuran (20 cm^3). The mixture was stirred at 25 °C for 24 h. The reaction mixture was quenched with aqueous sodium sulfate at 0 °C, the precipitated salts were filtered off and washed with dichloromethane (100 cm^3) and ethyl acetate (50 cm^3) and the combined filtrate and washings were evaporated to dryness. Flash chromatography [gradient elution, ethyl acetate (0–50%) in cyclohexane] gave 2,3-*bis*(*mercaptomethyl*)-7-*oxabicyclo*[2.2.1]*hept*-5-*ene* **28** as an oil (0.42 g, 89%) (Found: M^+, 188.0331. $C_8H_{12}O^{32}S_2$ requires *M*, 188.0330); δ(400 MHz) 1.46 (2 H, dd, *J* 8.6 and 7.1, SH), 1.72–1.78 (2 H, m, 2-H and 3-H), 2.38–2.50 (2 H, m, one of CH_2SH), 2.75–2.87 (2 H, m, one of CH_2SH), 4.95 (2 H, 1-H and 4-H) and 6.39 (2 H, 5-H and 6-H).

(*e*) The dithiol **28** (0.35 g, 1.86 mmol) in dichloromethane (15 cm^3) was added slowly to a suspension of manganese(IV) oxide (1.09 g, 11.4 mmol) in dichloromethane (15 cm^3) at −20 °C under argon. The reaction mixture was stirred at −20 °C for 12 h then filtered. The filtrate was evaporated to leave the *title compound* **7** (0.30 g, 88%) as a yellow oil (Found: M^+, 186.0172. $C_8H_{10}O^{32}S_2$ requires *M*, 186.0173); δ(200 MHz) 2.04–2.12 (2 H, m), 2.94–3.10 (4 H, m), 4.63 (2 H) and 6.38 (2 H); *m*/*z* 186 (18%), 149 (11%), 118 (78%), 85 (44%), 68 (65%) and 56 (84%).

Pyrolysis of the Disulfide **7**.—Vapour phase pyrolysis was carried out in a similar way to that used for disulfide **5**. The disulfide **7** (300 mg) was vapourised through a tube maintained at 650 °C and 0.1 mmHg and the pyrolysate was condensed on a surface cooled to −196 °C which had previously been coated with a film of *N*-phenyltriazolinedione (70 mg) in acetone. The pyrolysis was discontinued after 4 h when 90 mg of the disulfide **7** had vapourised. The condensate was allowed to warm to room temperature. The red solution was evaporated to dryness and the residue was subjected to preparative layer chromatography (silica) which gave (with ethyl acetate–cyclohexane, 1:4) the cycloadduct **29** (32 mg, 29%), m.p. 157–160 °C (lit.,[18] 157–160 °C), which was identified by comparison with a specimen prepared from butadiene and *N*-phenyltriazolinedione.

9,10-*Dihydroanthracene*-9,10-*bispyridinium Dibromide* **31**.—9,10-Dibromo-9,10-dihydroanthracene **30** was prepared by the method of Barnett and Cook[19] from anthracene and bromine, but with tetrachloromethane as solvent in place of carbon disulfide. The dibromoanthracene was isolated as an unstable solid which gave 9-bromoanthracene when an attempt was made to record its NMR spectrum: δ[200 MHz; $(CD_3)_2SO$] 7.50–7.70 (4 H, m), 8.40 (2 H, br d) and 8.73 (1 H). To pyridine (25 cm^3) stirred at 0 °C was added the dibromide **30** (2.72 g, 8.04 mmol) in portions. After all the solid had been added, stirring was continued until a new precipitate appeared. This was filtered off to give a cream solid which was identified as the *title compound* **31** (2.79 g, 70%) (Found: C, 58.0; H, 4.0; N, 5.5. $C_{24}H_{20}Br_2N_2$ requires C, 58.1; H, 4.0; N, 5.6%); δ(200 MHz; D_2O) 7.42–7.47 (4 H, m), 7.50–7.59 (4 H, m), 7.61 (2 H, d, *J* 1.5, 9-H and 10-H), 8.06–8.14 (4 H, approx. t), 8.57–8.65 (2 H, approx. t) and 8.98 (4 H, approx. d, *J* 6.3).

9,10-*Dihydroanthracene*-9,10-*bisisothiouronium Dibromide* **32**.—Thiourea (1.48 g, 0.019 mol) was dissolved in a mixture of acetonitrile and xylene at 0 °C, an ultrasonic bath being used to aid solution. The dibromide **30** (3.30 g, 9.76 mol) was then added in portions to the rapidly stirred solution at 0 °C. A precipitate appeared which was filtered off, rapidly washed with dichloromethane and dried to give the title compound **32** (1.43 g, 30%) as an unstable solid; δ[200 MHz; $(CD_3)_2SO$; signals referenced to $(CH_3)_2SO$ signal at δ 2.49] 6.90 (2 H, 9-H and 10-H), 7.45–7.52 (4 H, m) and 7.65–7.75 (4 H, m). This compound rapidly decomposed in the solid or in solution to anthracene-9-isothiouronium bromide **33**; δ[200 MHz; $(CD_3)_2SO$] 7.64 (2 H, t, *J* 8.0), 7.77 (2 H, t, *J* 8.0), 8.25 (2 H, d, *J* 8.0), 8.46 (2 H, d, *J* 8.0) and 9.03 (1 H); *m*/*z* 253 ($C_{15}H_{13}N_2S^+$).

Acknowledgements

We thank the SERC for a Studentship (to J. E. W.), the Rohm and Haas Company for support and Dr. Zev Lidert for advice and discussion.

References

1 (*a*) K. Steliou, Y. Gareau and D. N. Harpp, *J. Am. Chem. Soc.*, 1984, **106**, 799; (*b*) K. Steliou, P. Salama, D. Brodeur and Y. Gareau, *J. Am. Chem. Soc.*, 1987, **109**, 926; (*c*) D. N. Harpp and J. G. MacDonald, *J. Org. Chem.*, 1988, **53**, 3812; (*d*) K. Steliou, Y. Gareau, G. Milot and P. Salama, *J. Am. Chem. Soc.*, 1990, **112**, 7819.

2 For a review of reactions in which S_2 has been suggested as an intermediate see C. R. Williams and D. N. Harpp, *Sulfur Reports*, 1990, **10**, 103.

3 (*a*) A. Orahovatz, M. I. Levinson, P. J. Carroll, M. V. Lakshmikantham and M. P. Cava, *J. Org. Chem.*, 1985, **50**, 1550; (*b*) M. Schmidt and U. Görl, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 887; (*c*) W. Ando, Y. Kumamoto and N. Tokitoh, *Tetrahedron Lett.*, 1987, **28**, 4833; (*d*) W. Ando, H. Sonobe and T. Alasaka, *Tetrahedron Lett.*, 1987, **28**, 6653; (*e*) K. C. Nicolaou, C.-K. Hwang, M. E. Duggan and P. J. Carroll, *J. Am. Chem. Soc.*, 1987, **109**, 3801; (*f*) K. C. Nicolaou, C.-K. Hwang, S. DeFrees and N. A. Stylianides, *J. Am. Chem. Soc.*, 1988, **110**, 4868; (*g*) J. E. Bishop, S. A. Dagam and H. Rapoport, *J. Org. Chem.*, 1989, **54**, 1876; (*h*) R. Sato, S.-i. Satoh and M. Saito, *Chem. Lett.*, 1990, 139.

4 F. Freeman, D. S. H. L. Kim and E. Rodriguez, *Sulfur Reports*, 1989, **9**, 207.

5 G. A. Urove and M. E. Welker, *Organometallics*, 1988, **7**, 1013; M. E. Raseta, S. M. Cawood, M. E. Welker and A. L. Rheingold, *J. Am. Chem. Soc.*, 1989, **111**, 8268.

6 J. L. Ripoll, A. Rouessac and F. Rouessac, *Tetrahedron*, 1978, **34**, 19.

7 W. G. Young, H. K. Hall and S. Winstein, *J. Am. Chem. Soc.*, 1956, **78**, 4338.

8 H. Miyake, S. Iguchi, H. Itoh and M. Hayashi, *J. Am. Chem. Soc.*, 1977, **99**, 3536.

9 Y. Kishi, T. Fukuyama and S. Nakatsuka, *J. Am. Chem. Soc.*, 1973, **95**, 6490, 6492.

10 E. H. Farmer and W. D. Scott, *J. Chem. Soc.*, 1929, 172; G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold and D. E. Williamson, *J. Org. Chem.*, 1973, **38**, 4109.

11 C. Y.-J. Chung, D. Mackay and T. D. Sauer, *Can. J. Chem.*, 1972, **50**, 3315.

12 B. Milligan and J. M. Swan, *J. Chem. Soc.*, 1965, 2901.

13 There is one earlier report of a 1,4-disubstituted benzodithiin decomposing in this manner: G. Cignarella and G. Cordella, *Gazz. Chim. Ital.*, 1974, **104**, 455.

14 M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.*, 1966, **88**, 4112.

15 J. Das, T. Vu, D. N. Harris and M. L. Ogletree, *J. Med. Chem.*, 1988, **31**, 930.

16 C. K. Hwang, W. S. Li and K. C. Nicalou, *Tetrahedron Lett.*, 1984, **25**, 2295.

17 R. Gray, L. G. Harruff, J. Krymowski, J. Peterson and V. Boekelheide, *J. Am. Chem. Soc.*, 1978, **100**, 2892.

18 R. C. Cookson, S. S. H. Gilani and I. D. R. Stevens, *J. Chem. Soc. C*, 1967, 1905.

19 E. de B. Barnett and J. W. Cook, *J. Chem. Soc.*, 1924, **125**, 1084.

20 E. de B. Barnett and J. W. Cook, *J. Chem. Soc.*, 1921, **119**, 901.

21 E. de B. Barnett, J. W. Cook and M. A. Matthews, *Recl. Trav. Chim. Pays-Bas*, 1925, **44**, 217.

22 M. J. Haddadin, B. J. Agha and B. F. Tabri, *J. Org. Chem.*, 1979, **44**, 494.

Paper 1/04946A
Received 25*th September* 1991
Accepted 9*th October* 1991