Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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To cite this Article Freeman, Fillmore , Kim, Darrick S. H. L. and Rodriguez, Eloy(1989) 'The Chemistry of 1,2-Dithiins', Journal of Sulfur Chemistry, 9: 3, 207 — 247
To link to this Article: DOI: 10.1080/01961778908048730
URL: http://dx.doi.org/10.1080/01961778908048730

Sulfur Reports
Volume 9(3), 1989, pp. 207–256
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THE CHEMISTRY OF 1,2-DITHIINS

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(Received April 27, 1988)

ABSTRACT: This report describes the bioactivity, the chemistry, and the synthesis of 1,2-dithiins, (*o*-dithiin, 1,2-dithia-3,5-cyclohexadiene) and its derivatives, including 1,2-benzodithiins, benzo[*c*]-1,2-dithiins (2,3-benzodithiins), dibenzo[*c*,*e*]-1,2-dithiins, 3,4-dihydro-1,2-dithiins, and 3,6-dihydro-1,2-dithiins.

Key words: 1,2-Dithiins, 1,2-benzodithiins, benzo[*c*]-1,2-dithiins (2,3-benzodithiins), dibenzo[*c*,*e*]-1,2-dithiins, 3,4-dihydro-1,2-dithiins, 3,6-dihydro-1,2-dithiins, singlet sulfur.

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I. INTRODUCTION

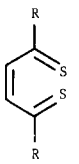
1,2-Dithiins (*o*-dithiins, 1,2-dithia-3,5-cyclohexadienes, **1**) are important compounds in the biological and chemical sciences.[1-21] This review, which covers the available literature to 1988, will discuss the bioactivity, the chemistry, and the synthesis of 1,2-dithiin (**1**)[1,2,5,10] and its derivatives. The chemistry of 1,4-dithiins (**2**),[1,7,9,11] and 4H-1,3-dithiins (**3**)[2,6] is not included.

1 R = H

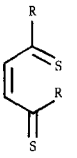
2

3

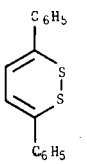
1,2-Dithiins (**1**, **4**) have a disulfide structure in cyclic conjugation and thus formally represent an 8π electron system which is isoelectronic with cyclooctatetraene. These structurally unique and theoretically interesting[2,22-25] compounds have been detected in plants and have been subjected to considerable study as antiviral compounds, which may be effective against herpes and against acquired immunodeficiency syndrome (AIDS).[13,26]



4a R = H



4b R = H



5

II. 1,2-DITHIINS

A. THEORETICAL STUDIES

Six-membered cyclic compounds with one or two sulfur atoms have a nonplanar structure. Thus, π-type calculations generally take into account the twisting of the p_π-orbitals. Although HMO and PPP calculations provide a negative π-bond order between the sulfur atoms in 1,2-dithiin (**1**), EHT calculations predict a σ-bond between the sulfur atoms. Consequently, the cyclic structure of 1,2-dithiin (**1**) should be more favored than the acyclic valence tautomers **4a** and **4b**. Spectral data also support the cyclic structure (**1**). The calculated π–π^* transition for 1,2-dithiin (**1**, 439 nm) compares well with the experimental value (451 nm, cyclohexane).[22] Transitions calculated for tautomeric structure **4a** are 376 (π–π^*) and 762 (weak, n–π^*) nm.

Frontier (HOMO–LUMO) orbital-interaction diagrams have been reported for 1,2-dithiin (**1**) and other cyclic sulfur-containing π-systems.[23]

Application of perturbation theory and the graph-theoretical definition of resonance energy have been combined and applied to 1,2-dithiins.[24] The negative graph perturbation theory resonance energy and the stabilizing terms that would arise from decreased conjugation are consistent with a nonplanar vinyl sulfide type structure for 1,2-dithiin (**1**).

Table 1. *Ab Initio* Molecular Orbital Calculations for 3,6-Dihydro-1,2-dithiin (7)

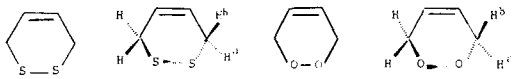
7

	Conformation	
	Planar C_{2v}	Nonplanar C_2
total energy (au) 3-21 G*	−945.39189	−945.41604
energy difference between C_{2v} and C_2 (kJ mol^{-1})	63.40	
total energy (au) MP2 6-31 G*		−950.75680
energy difference between C_{2v} and C_2 (kJ mol^{-1})		
r_{S-S} Å	2.097	2.049
r_{C-S} Å	1.826	1.818
r_{C-C} Å	1.503	1.515
$r_{C=C}$ Å	1.312	1.317
r_{C-Ha} Å	1.083	1.083
r_{C-Hb} Å		1.084
$r_{=C-H}$ Å	1.076	1.075
< H-C-H	107.62	107.92
< H-C=C	117.41	118.27
< C-S-S	108.83	97.89
< C-C=C	130.79	127.79
< C-C-S	120.38	114.14
dihedral angle CSSC	0	63.39
dihedral angle CCSS	0	52.57
dihedral angle CCCS	0	21.12
twist angle[a]	0	31.70

a) The twist angle between the S–S bond and the plane involving the four carbon atoms.

The chemical shifts of δ 5.97 and 6.13 for the parent 1,2-dithiin also suggest that **1** does not exist as any of the valence tautomers (**4a**, **4b**).[27-30] The heat of formation of 3,6-diphenyl-1,2-dithiin (**5**) supports a cyclic structure.[25]

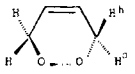
Molecular orbital studies of planar (C_{2v}) 3,6-dihydro-1,2-dithiin (**6**),[3,31] nonplanar (C_2) 3,6-dihydro-1,2-dithiin (**7**) and its derivatives,[3,31-33] 3,4-dihydro-3,6-dimethyl-4-(methylthio)-3-[2-(methylthio)ethenyl]-1,2-dithiin,[34] planar 3,6-dihydro-1,2-dioxin (**8**),[3,31] and nonplanar 3,6-dihydro-1,2-dioxin (**9**)[3,31, 35-37] have been reported (Tables 1 and 2).[3]



6 **7** **8** **9**

Ab initio molecular orbital calculations (6–31 G*)[31] show (Table 1) that the nonplanar conformational isomer of 3,6-dihydro-1,2-dithiin (**7**) is more stable than the planar isomer by 38.5 kJ mol^{-1}. Similarly *ab initio* calculations show that the nonplanar conformation of 3,6-dihydro-1,2-dioxin (**9**) is 45.2 kJ mol^{-1} more stable than the planar conformation (Table 2).[3]

Table 2. A Comparison of *Ab Initio* Calculated and Observed Bond Lengths (Å) and Bond Angles (Deg) of 3,6-Dihydro-1,2-dioxin (**9**)

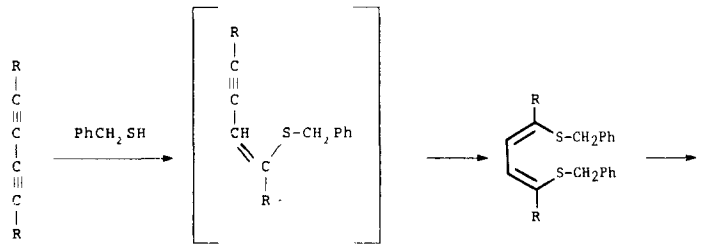
 **9**	Conformation		experimental value[11,12]
	Planar C_{2v}	Nonplanar C_2	
total energy (au) 3-21 G	−302.85020	−302.87631	
energy difference between C_{2v} and C_2 (kJ mol^{-1})	68.55		
total energy (au) MP2 6-31 G*		−305.44120	
energy difference between C_{2v} and C_2 (kJ mol^{-1}			
r_{O-O}	1.470	1.464	1.463
r_{C-O}	1.460	1.454	1.426
r_{C-C}	1.493	1.509	1.504
$r_{C=C}$	1.306	1.313	1.338
r_{C-H^a}	1.083	1.080	1.10
r_{C-H^b}		1.081	
$r_{=C-H}$	1.073	1.073	1.09
< H–C–H	108.51	109.63	109.28
< H–C=C	121.54	121.92	
< C–O–O	120.16	104.75	
< C–C=C	123.09	120.66	119.9
< C–C–O	116.75	109.75	110.3
dihedral angle COOC	0	80.25	80.0 ± 2
dihedral angle CCOO	0	57.39	
dihedral angle CCCO	0	16.61	
twist angle[a]	0	40.12	38.3

a) The twist angle between the O–O bond and the plane involving the four carbon atoms.

B. SYNTHESIS

Treating 1-hexyne with carbon disulfide catalyzed by cobalt bis(2-ethylhexanoate) and triethylaluminum in absolute dimethyl sulfoxide and absolute methylbenzene gave 1,2-dithiin (**1**) and 3,6-dibutyl-1,2-dithiin in 40% overall yield.[27] Analogously, from 1-hexyne and S_8 (S_α-cyclooctasulfane) a mixture containing **1**, 3,6-dibutyl-1,2-dithiin, 2,5-dibutylthiophene, 1,3,4-tributylbenzene, and 1,3,5-tributylbenzene was obtained.

The parent 1,2-dithiin (**1**) and its 3,6-disubstituted derivatives have been prepared from symmetric 1,3-butadiynes (**10**, eq. 1).[28-30] The synthesis of these derivatives was accomplished by nucleophilic addition of phenylmethanethiol to 1,3-butadiynes (eq. 1).



10 **11** **12**

Reductive debenzylation of **12** with sodium in liquid ammonia (−70 °C) gives the (Z,Z)-1,3-butadiene-1,4-dithiols (**13**), which on air oxidation in alkaline solution or oxidation with ferric chloride in methanol give 1,2-dithiins as deep red crystals. The parent 1,2-dithiin (**1**) is a nonaromatic labile red oil that easily polymerizes and splits off sulfur with the formation of thiophene.[28,38]

(1)

13

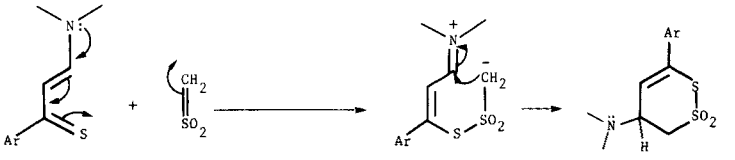
1	R = H	**16**	R = 4-$CH_3OC_6H_4$
5	R = C_6H_5	**17**	R = 4-biphenylyl
14	R = CH_3	**18**	R = 1-naphthyl
15	R = 4-$CH_3C_6H_4$	**19**	R = 2-thienyl

Unsymmetric 1,2-dithiins (R = C_6H_5, 4-$CH_3C_6H_4$; R = C_6H_5, 4-$CH_3OC_6H_4$) have been prepared by this method.[30] In some cases (R = CH_3, 4-CH_3C_{64}, 4-$CH_3OC_6H_4$) the monoaddition products **11** were isolated. The relatively unstable dithiols **13** were stored as the diacetyl compounds (**20**, eq. 2) from which they were regenerated in dilute alkaline solution.[28]

(2)

13 **20**

2-Aminovinyl thioketones (**21**, $-N<$ = morpholino, piperidino, anisidino) undergo 1,4-cycloaddition reactions with sulfene (**22**) to give 4-amino-6-aryl-3,4-dihydro-1,2-dithiin 2,2-dioxides (Ar = C_6H_5 (**24**), 4-BrC_6H_4 (**25**), 4-$CH_3C_6H_4$ (**26**), 4-$CH_3OC_6H_4$ (**27**), 41–61%).[39,40] Elimination of the amine occurs during the reaction of phenylsulfene (**28**) and the thioamide vinylogues (**21**) to give 3-aryl-6-phenyl-1,2-dithiin 1,1-dioxides (Ar = C_6H_5 (**29**), 4-BrC_6H_4 (**30**), 4-ClC_6H_4 (**31**), 4-$CH_3OC_6H_4$ (**32**), 37–53%).[39,40]



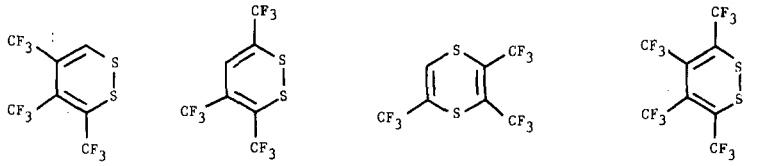
(3)

21 **22** **23** **24–27**

(4)

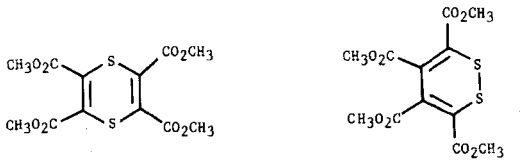
28 **29–32**

3,4,5-Tris(trifluoromethyl)-1,2-dithiin (**33**) or its 3,4,6-isomer (**34**) or 1,4-dithiin (**35**) is formed in low yield during the reaction of sulfur atoms with a 1:1 mixture of 3,3,3-trifluoro-1-propyne (**36**) and 1,1,1,4,4,4-hexafluoro-2-butyne (**37**) at 150 °C.[41] 3,4,5,6-Tetrakis(trifluoromethyl)-1,2-dithiin (**38**) is formed during the reaction of sulfur atoms with 1,1,1,4,4,4-hexafluoro-2-butyne (**37**).[41a] Disubstituted thiophenes and trisubstituted benzenes are the major products in these reactions. Similar results were obtained with $CF_3SC{\equiv}CSCF_3$.[41b]



33 **34** **35** **38**

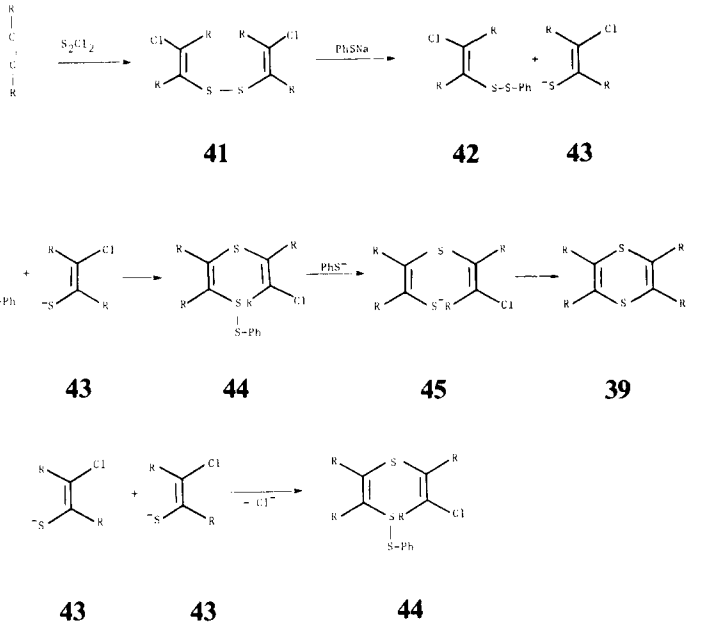
The formation of thiophenes from both 1,2-dithiins and 1,4-dithiins has led to some confusion in product identification in several reactions.[27-30,42-55] A structural reassignment to tetramethyl 1,4-dithiin-2,3,5,6-tetracarboxylate (**39**) as the product from the reaction of disulfur dichloride and dimethyl acetylenedicarboxylate, instead of the tetramethyl ester of 1,2-dithiin-3,4,5,6-tetracarboxylic acid (**40**), has been reported by Olsen and Snyder[42] (Scheme 1).



39 **40**

An important clue to the structures of 1,4-dithiins lies in their colors. Most known 1,2-dithiins are red with $\lambda_{max} < 450$ nm,[27-30] while the 1,4-isomers are generally colorless or yellow unless embedded in a planar, highly conjugated system.[46,47] The ^{1}H NMR spectrum of 1,4-dithiin **39** shows a singlet at δ 3.85 and the broad band decoupled ^{13}C NMR spectrum displays peaks from only three different carbon atoms (δ 53.6, 134.6, 161.8).[42]

Scheme 1.

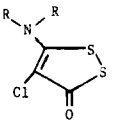


41 **42** **43**

42 **43** **44** **45** **39**

43 **43** **44**

1,2-Dithiins **47–51** [diethyl ester of 3,6-di-(1-piperidino-1,2-dithiin-4,5-dicarboxylic acid (**47**), dimethyl ester of 3,6-bis(*N*,*N*-diethylamino)-1,2-dithiin-4,5-dicarboxylic acid (**48**), dimethyl ester of 3,6-di-(1-morpholino)-1,2-dithiin-4,5-dicarboxylic acid (**49**), 3,6-di-(1-piperidino)-1,2-dithiin-4,5-dicarboxylic acid (**50**), 3,6-bis(*N*,*N*-diethylamino)-1,2-dithiin-4,5-dicarboxylic acid (**51**)] have been reported as the products from the alkaline cleavage of 1,2-dithiacyclopenten-3-ones **46**.[44,45] It may be possible that structures **47–51** are the corresponding 1,4-dithiins.[42]



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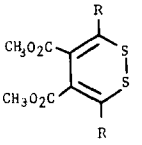
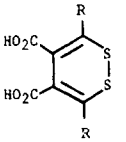


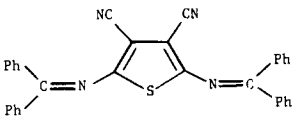
47 R = 1-piperidino
48 R = $N(C_2H_5)_2$
49 R = 1-morpholino



50 R = 1-piperidino
51 R = $N(C_2H_5)_2$

Yellow 3,4-dicyano-2,5-bis[(diphenylmethylene)amino]thiophene (**52**) and ruby-red prisms of 3,6-bis[diphenylmethylene)amino]-1,2-dithiin-4,5-dicarbonitrile (**53**, *cf.* **4**) were obtained from the reaction of tetracyanoethene (TCNE) and thiobenzophenone in

benzene or in chloroform.[54] Heat or sunlight converts 1,2-dithiin **53** to the thiophene derivative **52**. The ^{13}C NMR spectrum ($CDCl_3$, 32 °C) of **53** reveals a high symmetry: δ_C 114.5 for two C≡N, 156.9 for two C=N, s at 101.0 for 2 olefinic carbon atoms, s at 136.6 and d at 132.2, 129.7, 128.7 for four C_6H_5. The δ_C resonances (172.7 ppm) for the thiocarbonyl atoms in **53** are less shielded than those in imidazole-2-thiones (162–167 ppm),[55] more shielded than those in some thioamides (thiobenzopiperidide 199.6 ppm,[56] thioacetamide 207.2 ppm,[57]), and much more shielded than those in thioketones (thiobenzophenone 238.5 ppm,[54] thiocamphor 269.0 ppm[57]).



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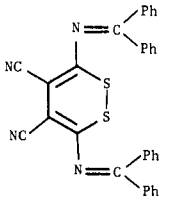
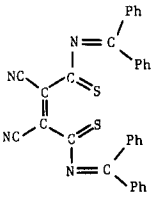


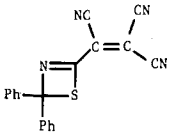
53a



53b

Formation of 1,2-dithiin **53** from thiobenzophenone and TCNE may involve a [2 + 2] cycloaddition of the activated nitrile group and the thiocarbonyl group to yield the 2 *H*-1,3-thiazete **54**. Electrocyclic ring opening of **54** affords tautomer **55**. Interestingly, the *cis-vic*-CN group in **54** is selected for the second sequence of cycloaddition.[54]

The degradation of 1,2-dithiin **53** to 1.7 equiv of benzophenone 2,4-dinitrophenylhydrazone underlines its structural relationship to **52**. The intermediacy of (Z)-**53b** provides a pathway for the conversion of 1,2-dithiin **53** to thiophene **52**. 1,5-Electrocyclization of **53b** gives rise to the zwitterion **56**, which extrudes the exocyclic sulfur to form the aromatic thiophene **52**.[38,54]



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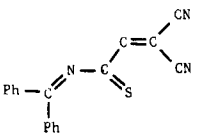

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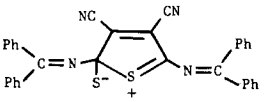
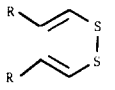


56

3,4-Dialkylthiophenes have been obtained by heating divinyl sulfides at 150–200 °C in the presence of potassium hydrogen sulfate.[58] The reaction is assumed to proceed via a

[3,3]-sigmatropic rearrangement of **57** to **58**, which are cyclopolymerized to **59**, whereupon potassium hydrogen sulfate-catalyzed elimination gives 3,4-dialkylthiophenes in about 60% yield. The possibility that 3,4-dialkylthiophenes are formed via enethiyl radicals cannot be excluded.



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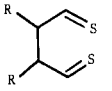

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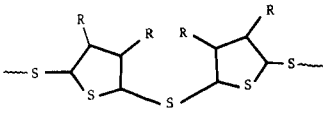
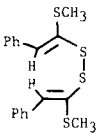


59

Divinyl disulfides (**60**), which are obtained by oxidative coupling of anions derived from dithio esters with diiodine, rearrange to the bisdithio esters **61**. Ring closure of **61** affords **62**.[59] 1,2-Dithiins may be intermediates in this reaction sequence.



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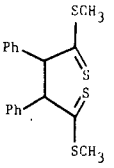

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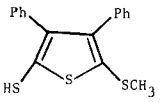
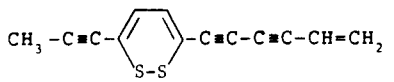


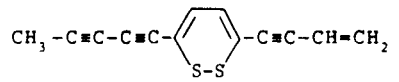
62

C. NATURALLY OCCURRING 1,2-DITHIINS

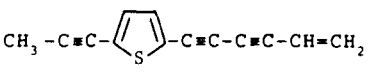
Anthropolgical studies[12] suggest that wild apes swallow leaves of *Aspilia (Asteraceae)* (the genus *Aspilia* includes approximately 90 species in Africa, Central America, Madagascar, South America, and Southern Europe) in a particular manner for possible therapeutic purposes. The major compounds in the young leaves of *Aspilia mossambicesis* and *Aspilia plurisetta* preferred by the wild chimpanzees are 3-(5-hexene-1,3-diynyl)-6-(1-propynyl)-1,2-dithiin, Thiarubrine A, **63**) and 3-(1,3-pentadiynyl)-6-(but-1-yn-3-enyl)-1,2-dithiin, Thiarubrine B, **64**).[13] These red-colored compounds absorb at 243, 435, and 490 nm. Thiarubrines A (**63**) and B (**64**), and the corresponding thiophene derivatives **65** and **66**, respectively, are present in the roots of *Chaenactis douglasii* and *Eriophyllum lanathum*.[14] Chemotaxonomic studies of naturally occurring polyalkynes indicate that the dithiacyclohexadiene polynes are primarily restricted to members of the sunflower family (*Asteraceae*.)[15]



63



64



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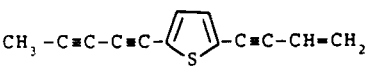
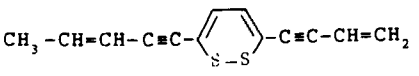


66

Several red-colored compounds [Thiarubrine A (**63**), Thiarubrine B (**64**), (E)-3-(3-buten-1-ynyl)-6-(3-penten-1-ynyl)-1,2-dithiin (**67**), (E)-3-(3,5-hexadien-1-ynyl)-6-(1-propynyl)-1,2-dithiin (**68**)] and the corresponding thiophene derivatives (**65**, **66**, **69**, **70**) have been isolated from several compositae.[15,16] These 1,2-dithiins (**63**, **64**, **67**, **68**) lose sulfur on TLC plates, on heating and on photolysis.[13-16] The occurrence and structure of Thiarubrine B (**64**) in *Eriophyllum caespitosum* and its structure have been discussed.[15-19]



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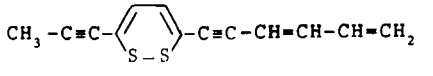
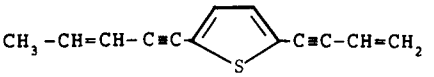
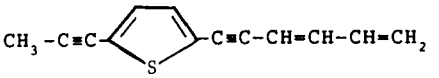


68



69

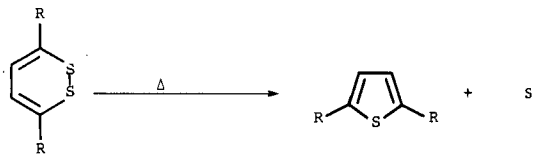


70

Thiarubrine A (**63**) and/or Thiarubrine B (**64**) are also found in roots of *Ambrosia artemisifolia*,[15b] in the aerial parts of *Pegolettia senegalensis*,[15c] in *Wedelia hookeriana*,[15d] in *Schkuhria multiflora*,[15e] in *Verbesina occidentalis*,[15f] in roots and overground parts of other *Verbesina* species,[15g] and in the roots of *Schkuhria senecioides*.[19] 3-(3-Buten-1-ynyl)-6-(3-penten-1-ynyl)-1,2-dithiin (**67**) is found in *Picradeniopsis woodhousei*,[16b] in the *Lasthenia* species,[16c] in *Oyedaea boliviana*,[16d] and in *Verbesina*.[16e] 3-(3,5-Hexadien-1-ynyl)-6-(1-propynyl)-1,2-dithiin 9**68**) has been found in the roots and aerial parts of *Melampodium divaricatum*.[16f]

D. REACTIONS

1,2-Dithiins readily eliminate sulfur when heated or irradiated to give the corresponding thiophenes.[13-16,28] The extrusion of sulfur may also be effected by heating with copper.[61-63] Heating 1,2-dithiin **68** at 80 °C affords the corresponding 2,5-disubstituted thiophene and sulfur.[18] On stirring an ethereal solution of **68** with mercury, the thiophene **70** and mercuric sulfide were isolated.[18] The extrusion of sulfur from 1,2-dithiins also predominates during attempted Diels-Alder reactions with maleic anhydride or tetracyanoethene (TCNE).[28]



(5)

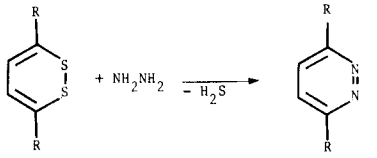
Treatment of **47** or **49** with copper powder or hydrogen-poor Raney nickel gives the corresponding thiophene derivatives (eq. 6).[44,45] The reaction of **47** with a Grignard

reagent also gives the corresponding thiophene derivative (eq. 6) together with other products.[44]

(6)

47 R = 1-piperidino
49 R = 1-morpholino

The 3,6-disubstituted 1,2-dithiins **5**, **15**, **16**, and **19** react with hydrazine in azabenzene or in *N*,*N*-dimethylmethanamide (DMF) to give the 3,6-disubstituted pyridazines **71**–**74**.[28-30]

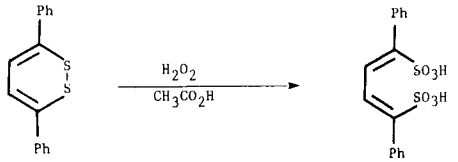


(7)

71 R = C_6H_5
72 R = 4-$CH_3C_6H_4$
73 R = 4-$CH_3OC_6H_4$
74 R = 2-thienyl

The 1,2-dithiins **5**, **15**, **16**, and **19** can be reduced with sodium tetrahydridoborate or with sodium in liquid ammonia to the corresponding thiols (**13**, *cf.* eq. 1).[28-30]

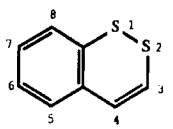
Oxidation of 3,6-diphenyl-1,2-dithiin (**5**) with hydrogen peroxide in glacial acetic acid leads to (Z),(Z)-1,4-diphenyl-1,3-butadiene-1,4-disulfonic acid (**75**).[28-30]



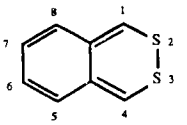
(8)

5 **75**

E. 1,2-BENZODITHIINS AND BENZO[c]-1,2-DITHIINS (2,3-BENZODITHIINS)

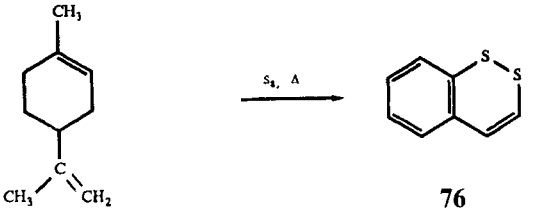


76



77

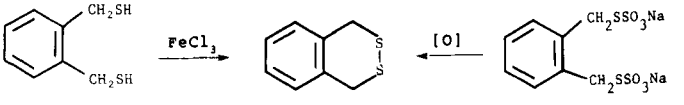
Refluxing limonene with S_8 for two hours gave a complex mixture containing ten monoterpenyl hydrocarbons and twenty-two sulfurated terpenyl compounds, *e.g.*, epithio derivatives, thiols, benzothiones, epitrithiomenthene, and 1,2-benzodithiin (**76**).[60]



(9)

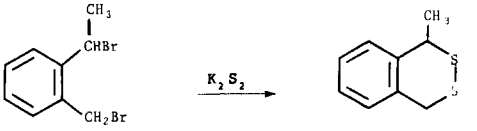
76

1,4-Dihydrobenzo[*c*]1,2-dithiin (1,4-dihydro-2,3-benzodithiin, 2,3-dithiatetralin, 3*H*,6*H*-benzo[*d*]-1,2-dithiin, **78**) is prepared via the oxidation of 1,2-bis(mercaptomethyl)benzene[61] or by treating the Bunte salt **79** with thiourea in hot dilute hydrochloric acid (eq. 10).[62] 1,4-Dihydro-1-methyl-2,3-benzodithiin (**80**) has also been prepared (eq. 11).[63]



(10)

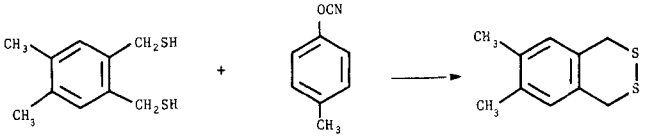
78 **79**



(11)

80

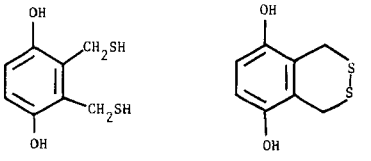
6,7-Dimethylbenzo[*c*]-1,2-dithiin (2,3-dithia-6,7-dimethyltetralin, **82**) is prepared according to eq. 12.[64]



(12)

81 **82**

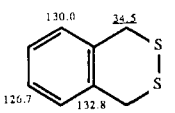
5,8-Dihydroxybenzo[*c*]-1,2-dithiin (**84**) has been isolated after the titration of the dithiol **83** in ether with 0.1 M diiodine solution containing one equivalent of azabenzene.[65] The diacetate of **84** also has been prepared.[65]



83 **84**

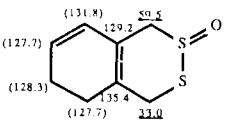
Proton magnetic resonance studies showed that 1,4-dihydro-2,3-benzodithiin (**78**), like 3,6-dihydro-1,2-dithiin (**6**), undergoes ring inversion more readily than 1,2-dithiane.[61,66]

Oae and coworkers[67] discussed the ^{13}C NMR spectra of **78**, benzo[*c*][1,2]-dithiin 2-oxide, (1,4-dihydro-2,3-benzodithiin 2-oxide, **85**), and benzo[*c*][1,2]-dithiin 2,2-dioxide (1,4-dihydro-2,3-benzodithiin 2,2-dioxide, **86**).[68] The chemical shifts in parentheses cannot be assigned definitively and the underlined chemical shifts are unusual.[67]



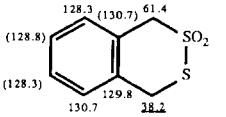
$J_{13C\,H}$

78



$J_{13C\,H}$

85

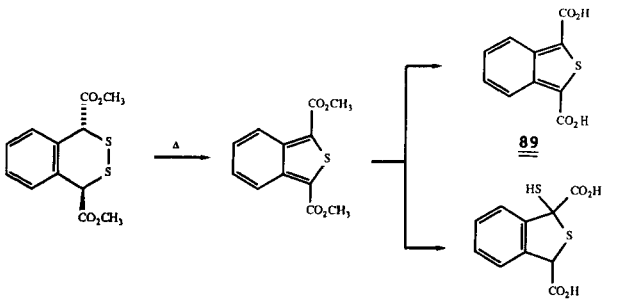


$J_{13C\,H}$

86

Benzo[*c*]-1,2-dithiin (**78**) is unstable in the presence of alkali and is polymerized photochemically in the presence of a number of ketones (*e.g.*, benzil, diacetyl, pyruvic acid), presumably to a linear polymer.[69]

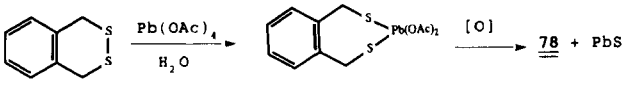
The *trans*-1,4-dimethyl ester **87** loses sulfur on heating to give **88** which may be hydrolyzed to **89** or **90** depending on the experimental conditions.[70,71]



87 **88** **90** (13)

Zinc reduces the 1,2-dithiin **78** to the corresponding dithiol (*cf.* eq. 10).[61] The thiosulfinate **85** and the thiosulfonate **86** are similarly reduced.

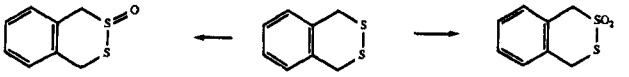
Treatment of 1,2-dithiin **78** with lead tetraacetate gives **91** which reacts with sulfur to regenerate **78**.[72,73]



78 **91** (14)

The 1,2-dithiin **78** is oxidized to the thiosulfinate **85**[61] or the thiosulfonate **86**.[61,68,74,75] 6,7-Dimethyl- (**82**) and 6,7-dimethoxybenzo[*c*]-1,2-dithiin can be oxidized to the corresponding thiosulfinates (6,7-dimethyl- and 6,7-dimethoxy-2,3-benzodithian 2-oxide).[76]

Similarly prepared were 3-benzodithian and naphthodithian derivatives. The minimum inhibitory concentrations of 6,7-dimethyl-2,3-benzodithian 2-oxide for three pathogenic fungi have been determined.[76]



(15)

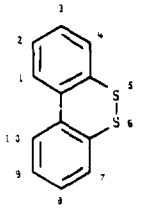
85 **78** **86**

Thiosulfonate **86** reacts with disodium sulfide to give the corresponding trisulfide **92** (84%) and with sodium 2-acetamidoethanethiolate to give disulfide sulfinate **93** (73%).[68,74,75]

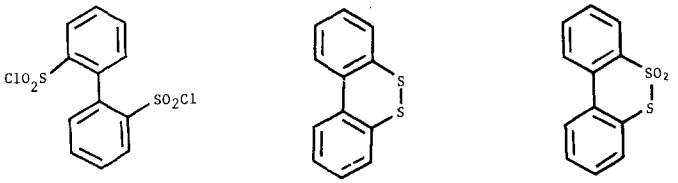
92 **93**

The relative rates of reactions of disulfides, including the 1,2-dithiin **78**, with methyl fluorosulfonate have been discussed.[77]

F. DIBENZO[c,e]-1,2-DITHIINS



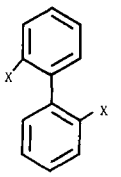
Reduction of biphenyl-2,2-disulfonyl dichloride (**94**) with zinc dust and hydrochloric acid gives the corresponding dithiol (50–60%) which is easily oxidized to the yellow dibenzo[*c*,*e*]-1,2-dithiin (2,2′-dithiobiphenyl, **95**).[78] Nitric acid oxidation of dibenzo[*c*,*e*]-1,2-dithiin **95** gives the thiosulfonic acid *S*-ester **96** (dibenzo[*c*,*e*]-1,2-dithiin 5,5-dioxide). Reduction of **94** with sodium sulfite gives not the expected biphenyl-2,2-disulfinic acid (**97**), but rather the cyclic thiosulfonate **96**.[78–82]

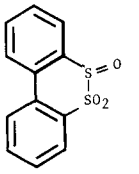


94 **95** **96**

Chau and Kice[83,84] have elucidated the mechanism of the sodium sulfite reduction of biphenyl-2,2-disulfonyl dichloride (**94**) into the cyclic thiosulfonate **96** instead of the expected biphenyl-2,2′-disulfinic acid (**97**).[81,82] It has been unambiguously shown[84] that the sequence of events involved in the conversion of **94** to **96** is as follows: (1) reduction

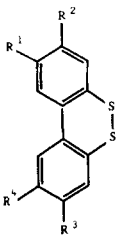
of **94** with excess sulfite leads to disodium biphenyl-2,2-disulfinate (**98**); (2) acidification of the aqueous reaction mixture containing **98** leads to the initial separation of disulfinic acid **97** as a second phase; (3) in this second phase, a considerable fraction of disulfinic acid **97** is present as the cyclic sulfinyl sulfone **99**; (4) excess sulfite (H_2SO_3 and $NaHSO_3$) reduces **97** to the cyclic thiosulfonate **96**. Thus, in contrast to acyclic sulfinic acids, the cyclic sulfinyl sulfone is favored with appropriately structured disulfinic acids.[84]

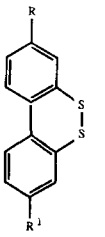




94 X = SO_2Cl **99**
97 X = SO_2H
98 X = SO_2Na

3,8-Dinitrodibenzo[*c*,*e*]-1,2-dithiin (**100a**) and 2,9-dinitrodibenzo[*c*,*e*]-1,2-dithiin (**100b**) have also been prepared by treating the corresponding sulfonyl chlorides (*cf.* **94**) with hydriodic acid in ethanoic acid at 23–25 °C.[85]





100a $R^1 = R^4 = H$; $R^2 = R^3 = NO_2$ **101**
100b $R^2 = R^3 = H$; $R^1 = R^4 = NO_2$
100c $R^1 = R^4 = H$; $R^2 = NO_2$; $R^3 = NH_2$
100d $R^1 = R^4 = H$; $R^2 = R^3 = NH_2$
100e $R^2 = R^3 = H$; $R^1 = NO_2$; $R^4 = NH_2$
100f $R^2 = R^3 = H$; $R^1 = R^4 = NH_2$

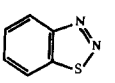
Reduction of **100a** with 55% hydriodic acid gave 8-amino-3-nitrodibenzo[*c*,*e*]-1,2-dithiin (**100c**), along with small amounts of 3,8-diaminodibenzo[*c*,*e*]-1,2-dithiin (**100d**).[86] The yield of **100d** increased with increasing amounts of hydriodic acid, and it became the major product when **100a** was reduced with stannous chloride and hydrochloric acid.

Reduction of 2,9-dinitrodibenzo[*c*,*e*]-1,2-dithiin (**100b**) with sodium hydrogen sulfite gave 9-amino-2-nitrodibenzo[*c*,*e*]-1,2-dithiin (**100e**) and 2,9-diaminodibenzo[*c*,*e*]-1,2-dithiin (**100f**).[87]

Seven substituted dibenzo[*c*,*e*]-1,2-dithiins (**101**) have been prepared from 8-amino-3-nitrodibenzo[*c*,*e*]-1,2-dithiin (**100c**) via diazotization followed by replacement of the

diazonium group.[87] The ethanoyl derivatives of **100e**, **100f**, and **101** have also been prepared.[87]

The reaction of 1,2,3-benzothiadiazole (**102**) with phenylthio radicals affords dibenzo[*c*,*e*]-1,2-dithiin (**95**), dibenzo-1,4-dithiin, thianthrene (**103**), and 2-(phenylthio)diphenyl disulfide (**104**).[88] Thermal decomposition of **102** in ethyl ethanoate at 220 °C gives dibenzo[*c*,*e*]-1,2-dithiin (**95**), thianthrene (**103**), dibenzothiophene (**105**), and thiophenol.[89]



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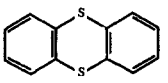

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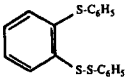
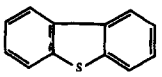


104

Thermolysis of 1,2,3-thiadiazoles leads to nitrogen and primary fragments, which are able to react via several pathways.[90] Among the products formed in the thermolysis of 1,2,3-thiadiazoles under nitrogen are dibenzo[*c*,*e*]-1,2-dithiin (**95**), 1,4-dithiin **106**, and compound **107**.



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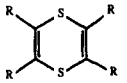

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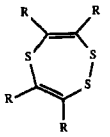
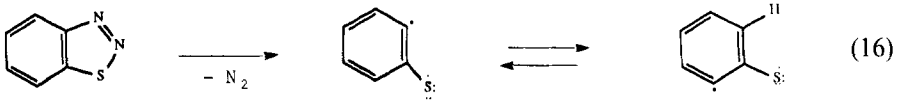


107

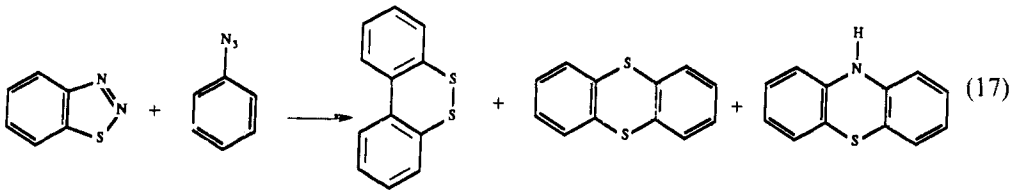
Photolysis and thermolysis of **102** gave dithiin **95**, **103**, **105**, diphenyl disulfide, and benzenethiol.[91,92] Carbon-13 labelling studies indicated that benzothiirene was not an intermediate.[91] The isotopomeric reactions were attributed to hydrogen shifts (eq. 16).



(16)

102 **108a** **108b**

Thermolysis of phenyl azide in the presence of 1,2,3-benzothiadiazole (**102**) gave dithiin **95**, thianthrene (**103**), and phenothiazine (**109**) in yields dependent on the phenyl azide concentration and the **102**-phenyl azide ratio.[93] A diradical mechanism was proposed with initial attack on the benzothiadiazole sulfur by a triplet nitrene.

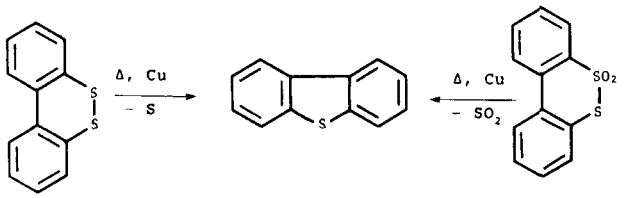


(17)

102 **95** **103** **109**

Dibenzo[*c*,*e*]-1,2-dithiin (**95**) obeys Beer's law in phenanthrene at 110 °C.[94]

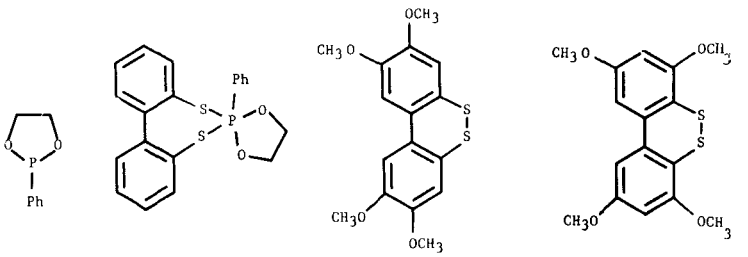
Sulfur is also extruded from dibenzo[*c*,*e*]-1,2-dithiins (eq. 18; *cf.* eq. 5, 6).[78-80,95] A sulfone group is eliminated in preference to a sulfur atom when thiosulfonate **96** is heated with copper.



(18)

95 **105** **96**

2-Phenyl-1,3,2-dioxaphospholane (**110**) reacts with **95** to give 2-phenylspirodibenzo[*d*,*f*]-1,3,2-dithiaphosphepin-2,2′-[1,3,2]dioxasphospholane (**111**, 100%) in ethanenitrile.[96] In cyanobenzene, dichloromethane, trichloromethane, and benzene, the reaction is reversible. Compound **111** is the second example of a sulfur-containing seven-membered ring spirophosphorane and the product [2-phenylspiro(1,3,2-dioxaphospholane-2,2′-naptho[1,8-*d*,*e*][1,3,2]-dithiaphosphorin)] from the reaction of **110** and 1,2-dithiaacenaphthene is the first example involving a sulfur-containing six-membered ring.[96]

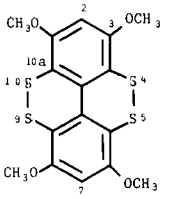


110 **111** **112a** **112b**

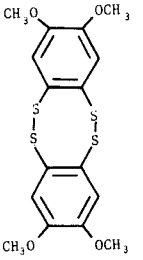
2,3,8,9-Tetramethoxy-2,2′-dithiophenyldiiodine, which is a compound with radical and polyiodide chains, was isolated from concentrated solutions of 2,3,8,9-tetramethoxydibenzo[*c*,*e*]-1,2-dithiin (**112a**) and diiodine as blue needles with brass-colored luster.[97,98] The crystal structure consists of stacks of (partially oxidized) **112a** units with alternating orientations and of disordered polyiodide chains in channels between these stacks. The **112a** molecule is nonplanar with a dihedral angle between the two phenyl rings of 25.1°

Cyclic voltammetry of **112** in ethanenitrile shows that they are oxidized in two one-electron steps. Electrolysis of **112a** in dichloromethane containing $Bu_4N^+ ClO_4^-$ or $NO^+ SbCl_6^-$ as supporting electrolyte gave the radical cation [2,2′-dithiobiphenyl]$^+$-[ClO_4^-] or [(2,2′-dithiobiphenyl)^2]$^+$[$SbCl_6^-$].[99] The tetrasulfides **113a** (1,2-benzodithiino[5,4,3-*cde*]-1,2-benzodithiin) and **113b** have also been electrolyzed.[99]

2,3,8,9-Tetramethoxydibenzo[*c*,*e*]-1,2-dithiin (**112a**) has been tested as an additive to



113a



113b

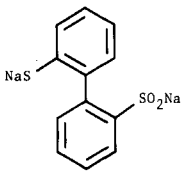
present overoxidation (overdoping) in the electrochemical oxidation of polyalkynes in ethanenitrile and dichloromethane.[100]

Dibenzo[*c*,*e*]-1,2-dithiin (**95**) has been reported to form polymers with 1,3-benzenedicarbonyl dichloride and 1,3-bis[(4-phenoxyphenyl)sulfonyl]benzene.[101]

An X-ray photoelectron spectroscopic study of symmetric acyclic aliphatic disulfides and cyclic (including **95**) or acyclic aromatic disulfides has been reported.[102]

It has been shown that the helicity of the optically active thiosulfonate **96** is the main factor in determining its twisting power in biphenyl nematic liquid crystals.[103,104]

Thiosulfonate **96** is reduced by sodium in liquid ammonia to the very hygroscopic 2′-mercapto-2-biphenylsulfinate (**114**, 98%).[105] Thiolates convert thiosulfonate **96** to disulfides **115** (cf. **93**) and sodium sulfide reacts with **96** to afford trisulfide **116** (cf. **92**).[68,74,76,106]



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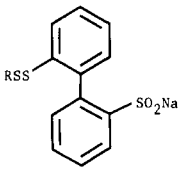

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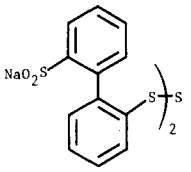


116

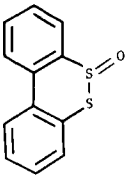
The equilibrium and rate constants for the reaction of thiolate ions with thiosulfonate **96** have been studied by Boduszek and Kice.[107]

The reactions of cyanide, sulfite, and thiolate ions with thiosulfonate **96** and thiosulfinate **117** have been compared.[108] In the thiosulfinate **117**-Me_3CS^- system, the rate constant for displacement by the sulfenate is 30,000 times faster than that for the corresponding displacement in the thiosulfonate **96**-Me_3CS^- system involving the sulfinate. This provided the first quantitative measure of how much more reactive a sulfenate ion is as a nucleophile than the corresponding sulfinate.

The racemization of thiosulfinate **117** in the presence of nucleophiles has been studied.[108]

Thiosulfonate **96** reacts rapidly with excess cyanide or sulfite ion in aqueous dioxane with opening of the thiosulfonate ring and formation of thiocyanate **118** or Bunte salt **119**.[83,109-111] Acidification of the final reaction solutions with carboxylic acid buffers of appropriate pH converts cyanide ion or sulfite ion to hydrogen cyanide or to hydrogen sulfite ion and one then observes quantitative regeneration of thiosulfonate **96**. The rates

of reaction of thiosulfonate **96** with cyanide ion ($k = 2.0 \cdot 10^3 M^{-1}s^{-1}$) or sulfite ion ($k = 0.95 \cdot 10^3 M^{-1}s^{-1}$) are not greatly different from the rates of reaction of *S*-phenyl benzenesulfonothioate (**120**, $7.8 \cdot 10^3$ (CN^-) and $7.8 \cdot 10^3$ ($SO_3^=$) $M^{-1}s^{-1}$) which may suggest the absence of significant ring strain in **96**.[112]



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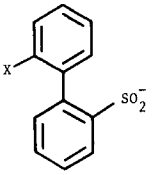
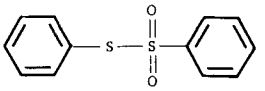


118 X = SCN
119 X = SSO_3^-

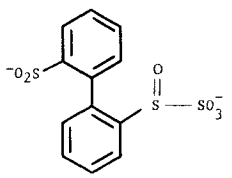


120

The rate of intramolecular displacement of cyanide ion from –SCN by $-SO_2^-$ ($k = 28.8\,s^{-1}$) is about 30 times faster than the rate of intramolecular displacement of sulfite ion from $-SSO_3^-$ by $-SO_2^-$ ($k = 0.0055\,s^{-1}$). This is striking because it is contrary to the belief sometimes expressed in the literature that Bunte salts are considerably more reactive as sulfenylating agents than thiocyanates.[83]

The rate constants for the forward ($k = 3.0 \cdot 10^5 M^{-1}s^{-1}$) and reverse ($k = 2.2 \cdot 10^{-4}s^{-1}$) reactions of the ring opening of the six-membered cyclic sulfinyl sulfone **99** by sulfite ion to the Bunte salt **121** ($K_{eq} = 1.40 \cdot 10^9 M^{-1}$) have been measured.[109] The equilibrium constant for the sulfinyl sulfone (**99**) reaction is 10^4 larger than K_{eq} ($K_{eq} = 1.7 \cdot 10^5 M^{-1}$) for thiosulfonate **96** which means that $\Delta G°$ for the ring opening of **96** by sulfite ion is $23\,kJ\,mol^{-1}$ less favorable than that of the ring opening in **99**. These data suggest that **96** is more than $23\,kJ\,mol^{-1}$ more stable than sulfinyl sulfone **99**, since a Bunte salt *S*-oxide functional group [$-S(O)S_3^-$] is less stable than a Bunte salt group ($-SSO_3^-$).[83] Acid hydrolysis of the Bunte salt **121** gives the thiosulfonate **96**.

The abnormally low rate and equilibrium constants for ring cleavage of thiosulfonate **96** by methoxide ion in methanol, the accelerating effect of dimethyl sufoxide, and the independence of the reverse reaction on solvent composition have been explained by a stepwise mechanism with **122** as an intermediate.[113]



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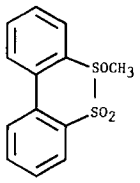
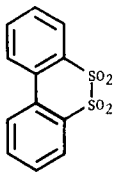


122

The rates of ring opening of the 1,1,2,2-tetraoxide **123** with nucleophiles have been determined.[110]

The disulfide (**115**) and trisulfide (**116**) sulfinate salts possess less antithyroid activity than 2-thiouracil.[68,74,76,106]

Dibenzodithiins (**124**; X and Y = H; halo, alkyl, amino, nitro, or acylamino; n = 0 or 2) are fungicides.[114] *Piricularia oryzae* in rice is controlled by 3,8-dimethyldibenzo[*c*,*e*]-1,2-dithiin (100 ppm).[114]



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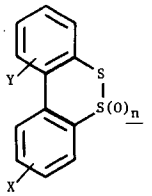
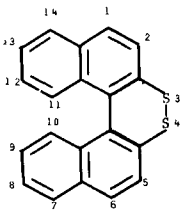


124

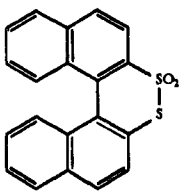
G. DINAPHTHO[2,1-c:1′,2′-e]-1,2-DITHIIN



125

Dinaphtho[2,1-*c*:1′,2′-*e*]-1,2-dithiin (1,1′-binaphthyl 2,2′-disulfide, **125**) is prepared from the corresponding disulfonyl dichloride.[78,115] Optically active **125** and thiosulfonate **126** have been prepared.[115] The (S)-configuration was assigned to (+)-**125** and (+)-**126**.[103,104,116] Both the Bijvoet X-ray method and an analysis of the circular dichroism spectrum of **125** confirmed that the (+)-isomer has the (S)-configuration, thus providing a reference for the correlation of configuration in the series of chiral 1,1′-binaphthyl 2,2′-sulfur-substituted derivatives.[116,117]

The atoms of each naphthalene nucleus of **125** are coplanar and the intramolecular dihedral angle between the mean planes of these nuclei is 56°.[116] As with **96**, it has been shown that the helicity of **125** is the main factor determining its high twisting power in biphenyl nematic liquid crystals.[103,104,118]



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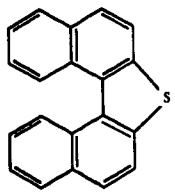
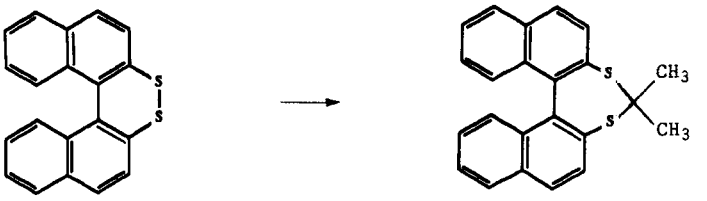


127

Dithiin **125** can be desulfurized with copper at 250 °C to give dinaphtho[2,1:1′,2′]thiophene (**127**).[78] The experimental conditions for dithiin **125** are more drastic than those

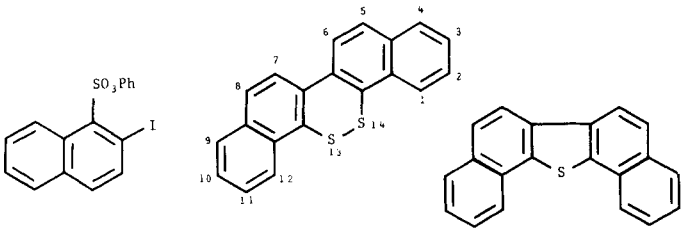
for desulfurization of simpler 1,2-dithiins (*cf.* eq. 4, 5). Reduction of dithiin **125** in the presence of propanone gives 4,4-dimethyldinaphtho[2,1-*b*:1′,2′-*d*]-1,3-dithiepine (**128**).[115]



(19)

125 **128**

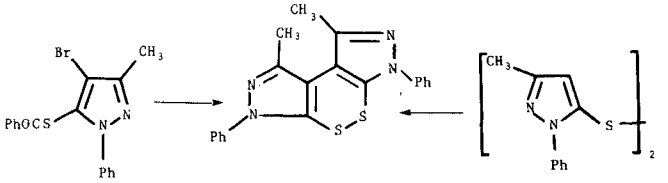
Dinaphtho[1,2-*c*:2′,1′-*e*]-1,2-dithiin (**130**) was prepared from **129**.[79] Heating dithiin **130** with copper gave dinaphtho[1,2:2′,1′]-thiophene (**131**).



129 **130** **131**

H. MISCELLANEOUS 1,2-DITHIINS

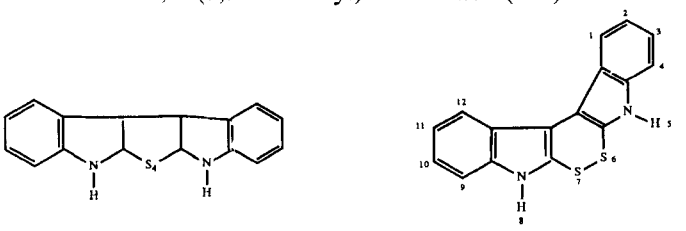
1,8-Dimethyl-3,6-diphenyl-1,2-dithiino[3,4-*c*:6,5-*c*′]dipyrazole (**134**) has been obtained by heating 5-benzoylthio-4-bromo-3-methyl-1-phenylpyrazole (**132**) with acid or with base or by distilling bis(5-methyl-1-phenyl-3-pyrazolyl) disulfide (**133**).[119]



(20)

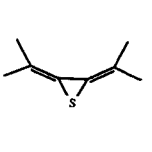
132 **134** **133**

5,8-Dihydro-1,2-dithiino[3,4-*b*:6,5-*b*′]diindole 2,2′-(3,3′-diindolyl) disulfide, **136**) was obtained by reduction of 2,2′-(3,3′-diindolyl) tetrasulfide (**135**).[120]



135 **136**

A boron trifluoride-catalyzed reaction of thiiranoradialene (**137**) afforded the dimerization products **138–141**.[121] The novel 1,2-dithia[6]radialene **139** underwent [2 + 4] cycloaddition to the strong dienophile **142** to give 5,11-dihydro-5,5,8,11,11-pentamethyl-1,4-bis(1-methylethylidene)-1*H*,4*H*,7*H*-[1,2]dithiino[4,5-*d*]1,2,4-triazolo[1,2-*a*]pyridazine-7,9(8*H*)-dione (**143**, 100%).



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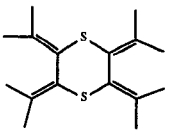

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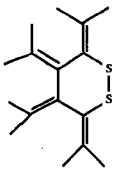

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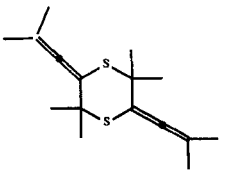

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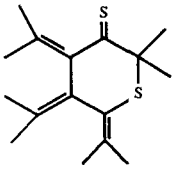

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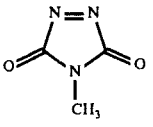
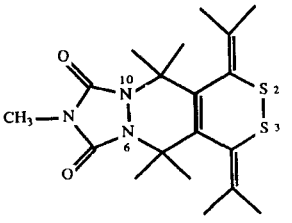
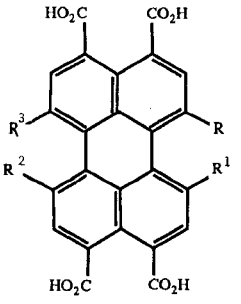


142

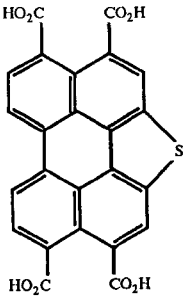


143

Heating the *tali*-[1-, 6-, 7-, and/or 12-]substituted perylene-3,4,9,10-tetracarboxylic acids **144** (R^2, R^3 = H; R, R^1 = SO_2, SO_2O) with sulfur in *N*-methylpyrrolidone gave the thienoperylene acid **145**. Similarly, **144** (R–R^3 = Br; R, R^2 = NO_2, R^1, R^3 = H; R^2 = Br, R, R^3 = H) gave the thienodithiinoperylene acid **146**, which may be decarboxylated to the parent heterocycle.[122]



144



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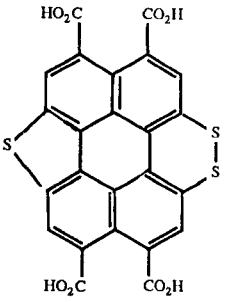
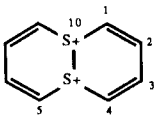


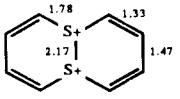
146

I. [1,2]DITHIINO[1,2-a]-1,2-DITHIINDIIUM



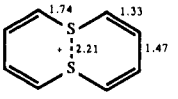
147

MINDO/3 molecular orbital studies[123] on 1,2-dithiino[1,2-*a*]-1,2-dithiindiium (**147**), the monocation **148**, and the naphthalene derivative **149** again emphasize the very poor ability of sulfur to form π bonds to carbon. The bond lengths and heats of formation are indicated on and below formulas **147–149**.



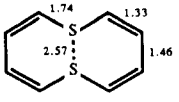
ΔH_f, 476.4

147



ΔH_f, 202.7

148



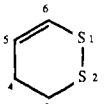
ΔH_f, 53.5

149

Although 1,2-dithiindiium **147** has not been prepared, octahydro derivatives of **147** have been synthesized.[124–126]

J. 3,4-DIHYDRO-1,2-DITHIINS

The preparation of 3,4-dihydro-1,2-dithiin (**150**) has not been reported.



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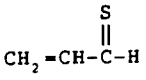
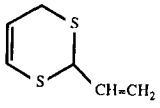
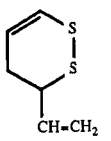


151

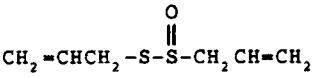


152

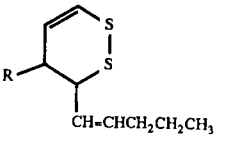
Diallyl disulfide decomposes quantitatively at 660 K in the gas phase to give an equimolar mixture of propene and propenethial (**151**).[127] On cool-trapping, propenethial (**151**) dimerized and the Diels-Alder adduct, predominantly the kinetic product 2-ethenyl-4*H*-1,3-dithiin (**152**), was isolated together with 3-ethenyl-3,4-dihydro-1,2-dithiin (**153**).[127–129] Treating propenal with hydrogen sulfide and ethyl orthoformate in the presence of $ZnCl_2$ gave the dithiins **152** and **153**.[130] *S*-3-Propenyl 2-propenethiosulfinate (allicin, **154**), which undergoes β-elimination to afford 2-propenesulfinic acid and propenethial (**151**), is also a precursor of the dithiins **152** and **153**.[131]



153



154

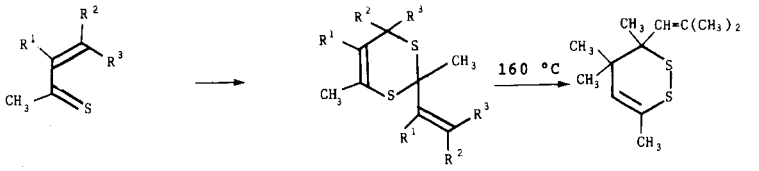


155 R = CH_3
156 R = C_3H_7

Dithiins **152** and **153** are found in the flavor components of cooked asparagus[132] and dithiin **153** is a component of garlic.[131,133-137] The formation of **153** in the aromatic components of cooked asparagus is assumed to involve reaction of hydrogen sulfide with propenethial (**151**)[130] which results from the thermal degradation of the *S*-methyl amino acid methionine.

3,4-Dihydro-4-methyl-3-(1-propenyl)-1,2-dithiin (**155**) and 3,4-dihydro-3-(1-pentenyl)-4-propyl-1,2-dithiin (**156**) have been prepared.[138,139]

Aliphatic α,β-unsaturated thioketones (**157**), *cf.* **151**) are unstable at 20 to 25 °C and exist in their dimeric form **158** or **159**.[140-143]

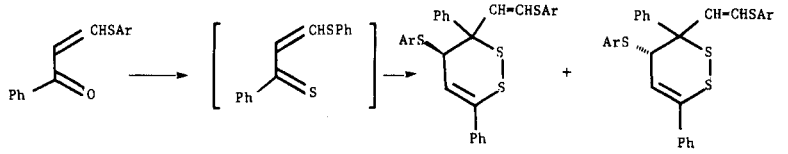


(21)

157a $R^1 = R^2 = R^3 = H$
157b $R^1 = R^3 = H$, $R^2 = CH_3$
157c $R^2 = R^3 = H$, $R^1 = CH_3$
157d $R^1 = H$, $R^2 = R^3 = CH_3$

158 **159**

Thionation of 1-phenyl-3-(phenylthio)-2-propene-1-one (**160a**) with Lawesson's reagent gave 3,6-diphenyl-4-(phenylthio)-3-[2-(phenylthio)-ethenyl]-3,4-dihydro-1,2-dithiin (**162a** and **163a**).[140] The ^1H NMR spectrum of **162a** showed doublets at δ 6.13 (J = 14.8 Hz) and 6.70 (J = 14.8 Hz). The assignment of a C-4 proton to the equatorial position is supported by the larger coupling constant (J = 5.2 Hz) between the C-4 and the C-5 protons as compared to **162a** and in comparison with those of the analogous 3,4-dihydro-1,2-dithiins.[144]

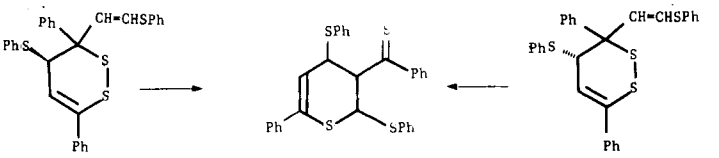


(22)

160a Ar = Ph
160b Ar = 4-$CH_3C_6H_4$
160c Ar = 4-ClC_6H_4

161 **162a–c** **163a–c**

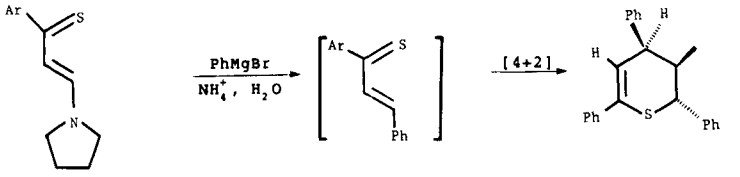
The 3,4-dihydro-1,2-dithiins **162a** and **163a** are converted to 1,4-diphenylhexane by Raney nickel reduction. Thermal isomerization of **162a** and **163a** affords 6-phenyl-2,4-bis(phenylthio)-3-thiobenzoyl-3,4-dihydro-2*H*-thiopyran (**164**).[140] The thermodynamic stabilities of compounds **162a**, **163a**, and **164** have been compared.[34,140]



(23)

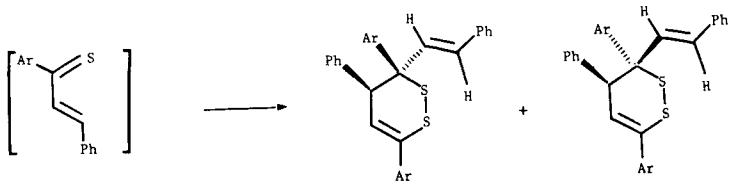
162a **164** **163a**

Treatment of the thioamide vinylogue **165** with phenylmagnesium bromide gives a green oil which contains, in addition to the thiopyran **167**, two stereoisomers of the 3,4-dihydro-1,2-dithiin **168**.[144] The dithiin **168** undergoes a retro-Diels-Alder reaction to regenerate **166** which dimerizes to thiopyran **167** (*cf.* eq. 3, 4, 20, 21).[39,40]



(24)

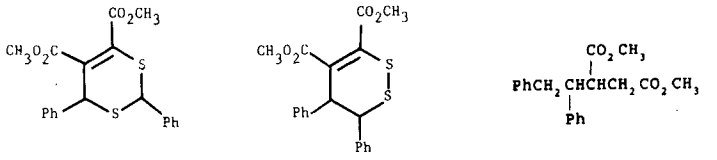
165 Ar = 4-ClC_6H_4 **166** **167**



(25)

166 **168a** (exo) **168b** (endo)

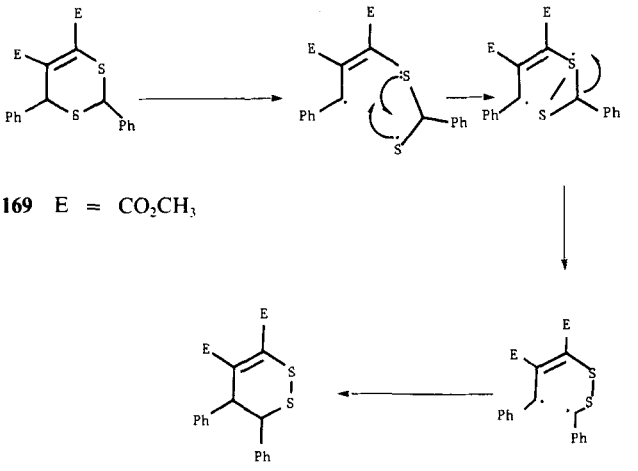
Thermolysis (185 °C) of dimethyl 2,4-diphenyl-1,3-dithiin-5,6-dicarboxylate (**169**) affords the isomeric 3,4-dihydro-3,4-diphenyl-1,2-dithiin-5,6-dicarboxylate (**170**).[145] The mechanism of this unusual rearrangement might involve fission of a C–S bond with formation of an allylic (and benzylic) diradical (Scheme 2). Dihydro-1,2-dithiin **170** showed an AB quartet centered at δ 4.43 (J_{AB} = 6.5 Hz) as well as signals for the ester



169 **170** **171**

protons (δ 3.48 and 3.84) and aromatic protons (δ 7.18 and 7.26). Desulfurization of dihydro-1,2-dithiin **170** with Raney nickel gave diester **171**.[145]

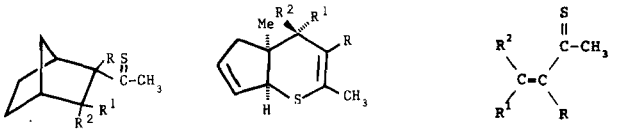
Scheme 2



169 E = CO_2CH_3

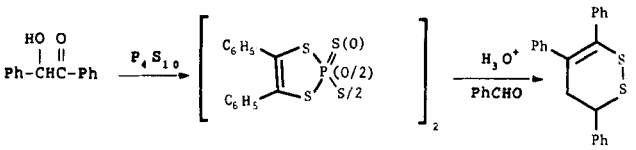
170

Thermolysis of the thioketones **172** (R = R^2 = H, R ≠ R^1 = R^2 = H, Me) and of the thiopyrans **173** (R = R^2 = H, R^1 = H, Me; R ≠ R^1 = R^2 = H, Me) gave $CH_3CSCR{=}CR^1R^2$ (**174**) which were detected at low temperature, but dimerized on warming to give the dithiins **158**.[146] 4*H*-1,3-Dithiin **158** (R = H, R^1 = R^2 = Me) isomerized at 190 °C to 3,4-dihydro-3,4,4,6-tetramethyl-3-(2-methyl-1-propenyl)-1,2-dithiin (**159**, *cf.* eq. 21).



172 **173** **174**

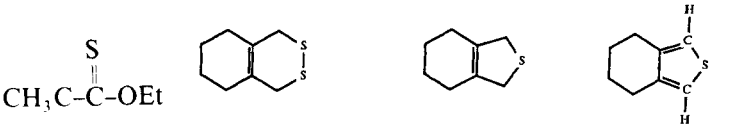
Heating benzoin with phosphorus pentasulfide in an inert solvent gives a compound ($C_{28}H_{20}O_2P_2S_5$) to which structure **175** has been assigned.[147] Solvolysis of **175** in the presence of phenylmethanal gave a compound to which structure **176** was tentatively assigned.



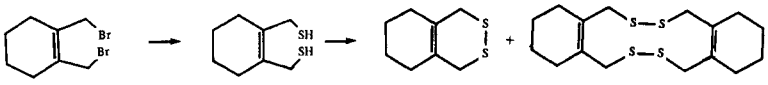
(26)

175 **176**

Irradiation of *O*-ethyl thioethanoate **177** gives (E)- and (Z)-2,3-diethoxy-2-butene and small amounts of 2,3-diethoxy-1-butene, 2,3-diethoxy-1,3-butadiene, 1-ethoxy-1-ethanethiol, monoatomic sulfur, and diatomic sulfur.[148] The sulfur so generated adds to 1,2-dimethylenecyclohexane to give 1,4,5,6,7,8-hexahydro[*d*]-1,2-dithiin (**178**), 1,3,4,5,6,7-hexahydrobenzo[*c*]-thiophene **179**, and 4,5,6,7-tetrahydrobenzo[*c*]-thiophene (**180**). Dithiin **178** and its dimer **183** were prepared according to eq. 27.[148]

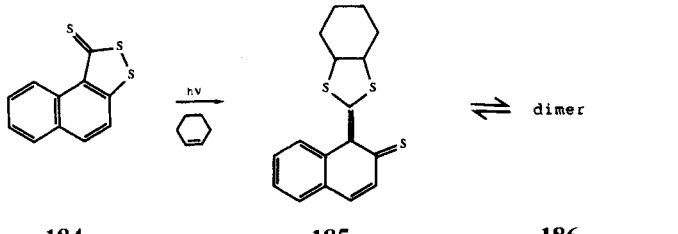


177 **178** **179** **180**

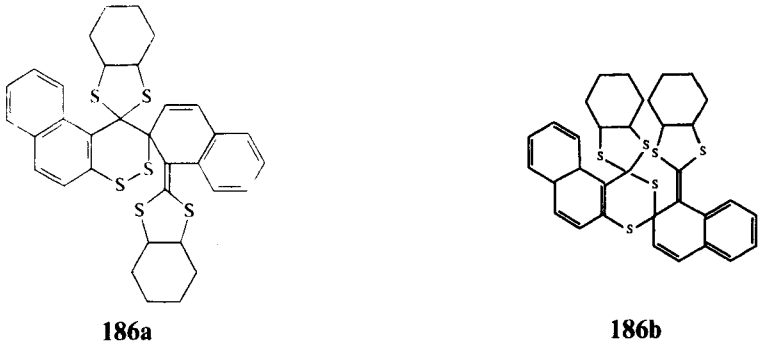


181 **182** **178** **183** (27)

Photolysis of naphtho[1,2-*d*]-1,2-dithiole-3-thione (**184**) with cyclohexene led to a deep red solution, the TLC of which showed the presence of a single product (**185**) together with a small amount of starting thione (**184**).[149] Work-up of the reaction mixture resulted in the isolation of a yellow dimeric compound (**186**) in addition to the monomeric red product **185**. Structure **186a** or **186b** (2 + 4] adduct) was suggested for the dimer.[149] The mutual conversion between **185** and **186** is the first example of a reversible thermochromic system where both monomeric and dimeric *o*-quinonoid compounds can be isolated.[149]



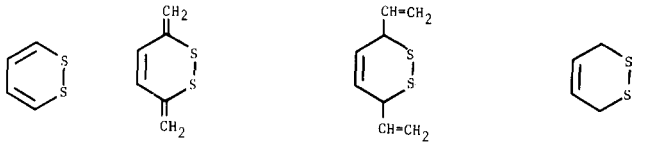
184 **185** **186** (28)



186a **186b**

K. 3,6-DIHYDRO-1,2-DITHIINS

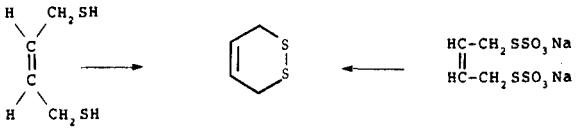
Frontier (HOMO–LUMO) orbital-interaction diagrams have been shown for cyclic sulfides and disulfides, including **1**, 3,6-dimethylene-3,6-dihydro-1,2-dithiin (**187**), and 3,6-diethenyl-3,6-dihydro-1,2-dithiin (**188**).[23]



1 **187** **188** **189**

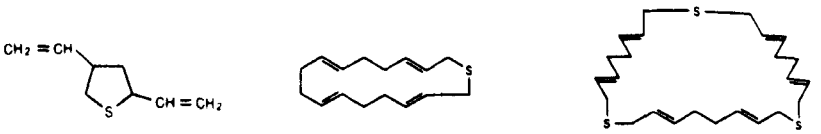
3,6-Dihydro-1,2-dithiin (**189**) is found in garlic[101,102] and in the aroma of cooked asparagus.[132]

3,6-Dihydro-1,2-dithiin (**189**) is obtained by treating (Z)-2-butene-1,4-dithiol (**190**) with ferric chloride[150] or by heating the Bunte salt **191** with sodium sulfide at 80 °C.[151] (Z)-1,2-Dichloro-2-butene reacts with disodium disulfide to give **189** (55–60%).[152] The ^{1}H NMR spectrum of **189** shows resonances at δ 3.22 (d, 2H, J = 2.1 Hz) and 5.95 (t, 4H, J = 2.1 Hz). 3,6-Dihydro-1,2-dithiin (**189**) is unstable and polymerizes readily.

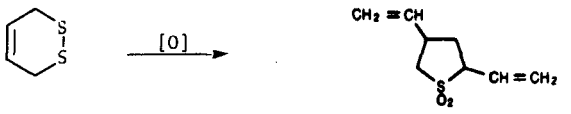


190 **189** **191** (29)

Treatment of 1,3-butadiene with sulfur, catalyzed by Pd(acac)-PPh_3-$AlEt_3$ (1:3:4) in absolute methylbenzene (10 h at 130 °C) in an argon atmosphere, gave dithiacyclohexene **189**, a mixture of (E)- and (Z)-2,4-diethenylthiophane (**192**), (E,E,E,E)-1-thia-3,7,-11,15-cycloheptadecatetraene (**193**), and the symmetrical trissulfide **194** in 80% overall yield.[153] Oxidation of **189** by Me_3COOH-$W(CO)_6$ (1 H at 80 °C) gave the unique (E)- and (Z)-sulfolane derivative **195** (99%).[153]

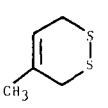


192 **193** **194**



189 **195** (30)

4-Methyl-3,6-dihydro-1,2-dithiin (**196**) is obtained by treatment of 2-methyl-1,3-butadiene and 3-methyl-3-sulfolene in propanone containing hydrogen sulfide, and catalytic amounts of 1,4-dihydroxybenzene and water at 140 °C, with sulfur dioxide under pressure.[154] Under similar experimental conditions, 2-methyl-1,3-pentadiene in propanone afforded 3,5-dimethyl-3,6-dihydro-1,2-dithiin (**197**, 20%).[154]



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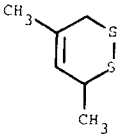
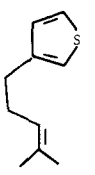
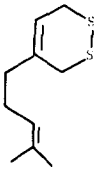


197

Steam-distilled hop oils (from hops dressed on the bine with sulfur) have been shown to contain 3-(4-methylpent-3-enyl)thiophene (**198**), 4-(4-methylpent-3-enyl)-3,6-dihydro-1,2-dithiin (**199**), together with the corresponding trisulfide (**200**) and tetrasulfide (**201**).[155-157] A mixture of these compounds was formed when myrcene (**202**) was treated with sulfur under a variety of photolytic conditions.[156]



198



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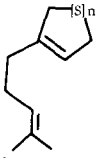
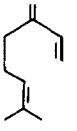
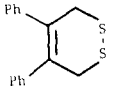


200 n = 3
201 n = 4



202

Reaction of (E)- or (Z)-1,4-dibromo-2,3-diphenyl-2-butene with sodium polysulfide in DMF gave a mixture of 4,5-diphenyl-3,6-dihydro-1,2-dithiin (**203**), 3,4-diphenylthiophene (**204**), and the cyclic tetrasulfide **205** (6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin).[158a] A four-step synthesis of **203** from 2,3-diphenylmaleic anhydride has been reported.[158b]



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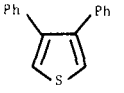

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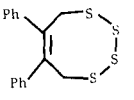
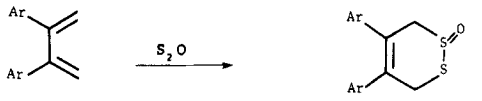


205

Oxidation of **203** with performic acid gave 4,5-diphenyl-3,6-dihydro-1,2-dithiin 1-oxide (**206**), which prefers the boat conformation.[158] Disulfur monoxide (S_2O) reacts with 2,3-disubstituted butadienes to form 4,5-disubstituted 3,6-dihydro-1,2-dithiin oxides (**206**, **207**).[158] When the dithiin 1-oxide **206** was treated with coordinatively unsaturated transition metal complexes, a transition metal-disulfur monoxide complex and 2,3-diphenyl-1,3-butadiene were isolated.[158b] These compounds are cyclic analogues of allicin (**154**), and oxide **206** shows bacteriostatic and fungistatic properties similar to **154**.[158]



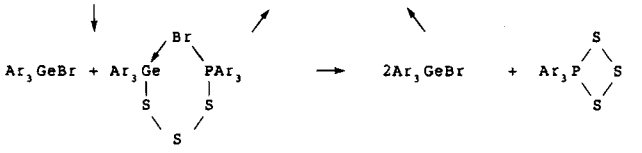
(31)

206 Ar = C_6H_5
207 Ar = 2-$C_{10}H_7$

Steliou, Gareau, and Harpp[159] have described a Group 14 metal assisted procedure for the preparation and Diels-Alder trapping of diatomic sulfur (S_2), which is different from the highly reactive form of activated elemental sulfur.[160-170]

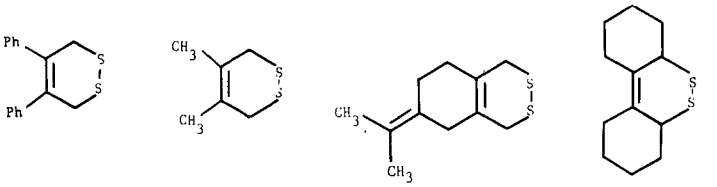
$$Ar_3MSSSMAr_3 + Ph_3PBr_2 \rightarrow 2\,Ar_3MBr + Ph_3P{=}S + S_2$$

208 M = Ge, Si



(32)

Treatment of the trisulfides **208** with triphenylphosphine dibromide (eq. 32) in the presence of conjugated dienes led to formation of the corresponding Diels-Alder adducts **203** (20%), **209** (35%), **210** (35%), and **211** (50%).[159-161]

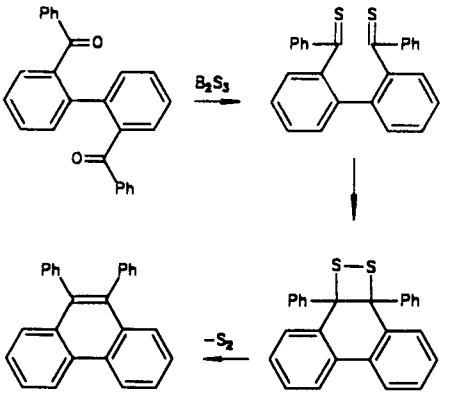


203 **209** **210** **211**

The Diels-Alder adducts **209–211** are particularly thermally sensitive to polymerization and are not prone to rearrange to the corresponding bis(episulfides).[159]

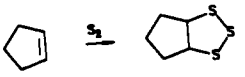
Steliou and coworkers[160,161] have developed an alternate synthetic method (eq. 33) that affords diatomic sulfur (S_2) by an unprecedented intramolecular carbon–carbon bond-forming reaction. Since S_2 is generated at 80–131 °C in this alternate procedure, the Diels-Alder trapping is considerably more efficacious than that observed at the temperature range (0–44 °C) possible with the organometallic method.[159] Improved yields are observed for **203** (85%), **209** (60%), **210** (75%), and **211** (70%). The all-trans isomer of 2,4-hexadiene gave the predicted *cis*-2,5-dimethyl-3,6-dihydro-1,2-dithiin (**209**) and none of the other adduct.[161]

Although cyclohexene does not react with singlet sulfur, strained cycloalkenes react to give epitrisulfides (eq. 34–38). Steliou and coworkers[161] have proposed a mechanism for epitrisulfide formation (eq. 39).



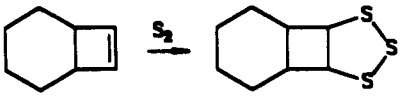
(33)

212



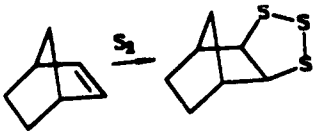
(34)

213



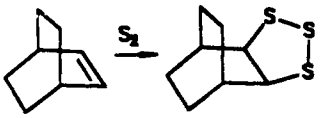
(35)

214



(36)

215



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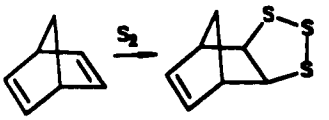
216



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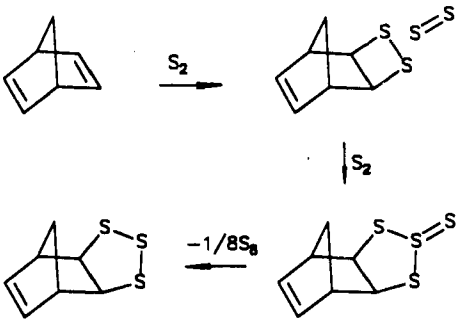
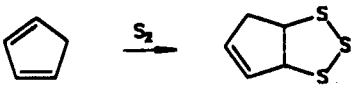
217



(39)

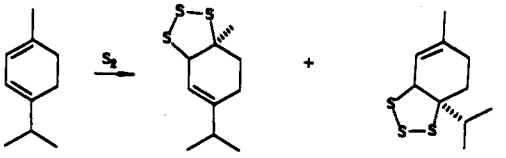
217

Steliou and cowrkers[161] also obtained bicyclic trisulfides from the reaction of singlet sulfur and cyclic 1,3-dienes (eq. 40–42). It was suggested that the Diels-Alder adduct is formed. Insertion of singlet sulfur into the adduct, followed by a 3,3-sigmatropic rearrangement and extrusion of elemental sulfur lead to the bicyclic trisulfide (eq. 43).[161,162]



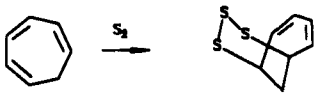
(40)

218



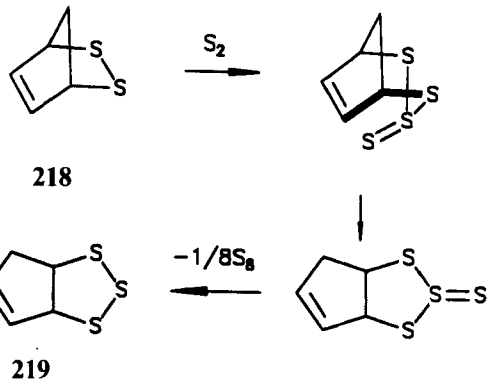
(41)

219 **220**



(42)

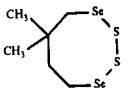
221



(43)

218 **219**

Schmidt and Görl[168] observed that 5,5-dimethyl-1,2-dithia-3,7-diselenocycloheptane (**220**) undergoes thermal decomposition with ring contraction and formation of singlet sulfur and 4,4-dimethyl-1,2-diselenocyclopentane (**221**). Heating **220** in the presence of 1,3-dienes in boiling chlorobenzene gave adducts **199**, **203**, (54%), **209**, (48%) and **211** (48%).



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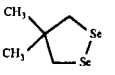

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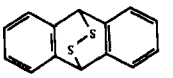
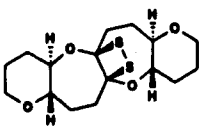


222

Ando and coworkers[166,167] observed that the novel 9,10-epidithio-9,10-dihydroanthracene (**222**) generated singlet diatomic sulfur which was trapped with conjugated dienes to afford adducts **203** (25%) and **211** (48%). No adduct was obtained with norbornene, and bisadamantylidene and bis(bicyclo[3.3.1]non-9-ylidene) gave the corresponding episulfides.

Nicolaou and coworkers[169,170] reported that the stable 1,2-dithietane (dithiatopazine, **223**) transfers sulfur atoms to suitable acceptors. Heating (100 °C) 1,2-dithietane **223** with 2,3-diphenyl-1,3-butadiene in methylbenzene gave adduct **203** (25%), tetrasulfide **224** (28%), and olefin **225** (90%). Under similar experimental conditions, the highly strained alkyne **226** gave the dithietene **227** (66%) and an unidentified product.



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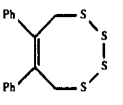

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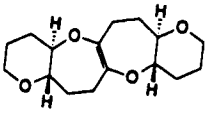

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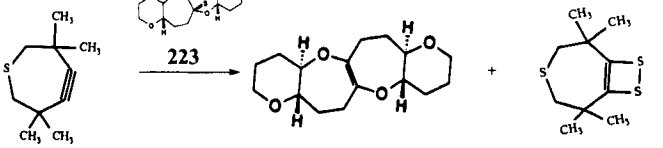
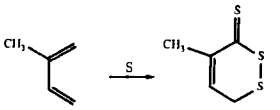


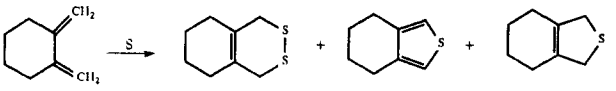
226 **225** **227**

(44)

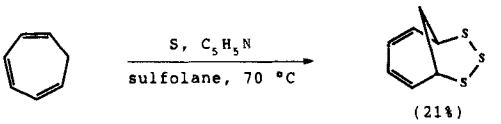
Steliou and coworkers[161,162] and Harpp and MacDonald[163] have taken the absence of episulfide or thiophene derivatives in their product mixtures as evidence for the generation of singlet sulfur rather than "activated elemental sulfur" (eq. 45–50).[171–179]



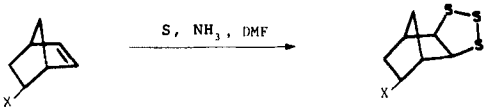
(45)



(46)

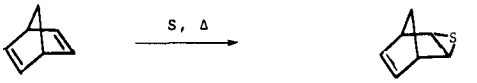


(47)

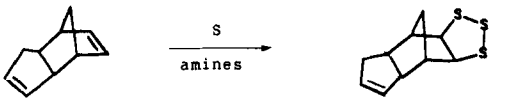


(48)

X = H **215** (86%)
X = =CHCH$_3$ (71%)

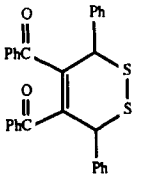


(49)



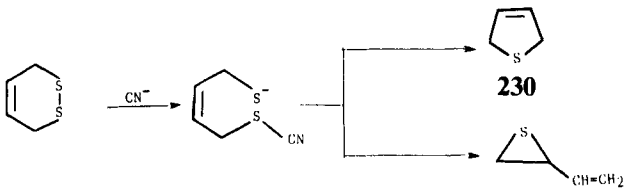
(50)

4,5-Dibenzoyl-3,6-dihydro-3,6-diphenyl-1,2-dithiin-4-ene (**228**) has been characterized as one of the four products isolated in the thermolytic reaction of benzalacetophenone (chalcone, $C_6H_5CH{=}CHCOC_6H_5$) with sulfur.[180]



228

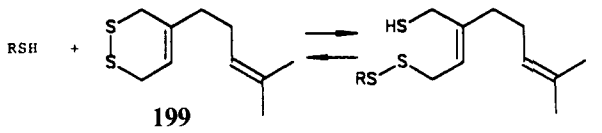
3,6-Dihydro-1,2-dithiin (**189**) undergoes cleavage with cyanide ion to afford 2,5-dihydrothiophene (**230**) and 2-ethenylthiiran (**231**).[152]



189 **229** **230** **231**

(51)

Myrcene disulfide (**199**) was treated with phenylmethanethiol, cysteine, and 2-methyl-2-propanethiol in methanol containing a catalytic amount of sodium hydroxide.[161] Nuclear magnetic resonance analysis showed that the equilibrium was to the left after a week with phenylmethanethiol or cysteine, and that 2-methyl-2-propanethiol was irreversibly exchanged in less than 10 hours (eq. 46).

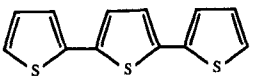


199 (46)

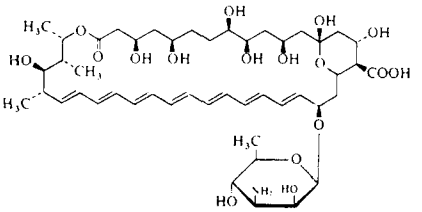
R = $PhCH_2$ R = *t*-Bu
R = $CH_2CH(NH_2)CO_2H$

L. BIOACTIVITY

The leaves of *Aspilia mossambicesis* consumed by wild apes are used by African natives for the treatment of abdominal pains, intestinal worms, and skin infections. A species of *Chenactis* was found to be used for a variety of medicinal purposes by various native North Americans, in particular, for treatment of sores and wound infections. Preliminary findings on the action of Thiarubrine A (**63**) (in the dark and light) on a variety of bacteria, fungi, viruses, and nematodes have been reported.[14] Thiarubrine A (**63**) is as effective as the strong photosensitizer α-terthienyl (α-T, **232**), which is effective against *Candida albicans, Staphylococcus albus, Mycobacterium phlei, Bacillus subtilis, Streptococcus faecalis*, and *E. coli* at a concentration of 0.1 to 1.0 ppm.[13,20] It is as effective against *Candida albicans* as fungizone (amphotericin B, **233**) at a concentration of 1 ppm in the dark or 0.1 ppm in light.



232

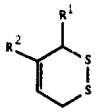


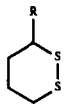
233

Thiarubrine A (**63**) has also been evaluated for its antiviral properties in the presence and absence of UV radiation (UV-A).[21] Two mammalian viruses, murine cytomegalovirus and Sindbis virus, both of which possess membranes, were extremely sensitive to the compound, but only in the presence of UV-A radiation. The bacteriophage T4 was slightly affected in the presence of UV-A radiation, whereas the

bacteriophage M13 was completely unaffected. These studies suggest that a photoactivated species of Thiarubrine A (**63**) is the active constituent. Although α-T (**232**) and Thiarubrine A (**63**) have significant antiviral activity at 10^{-5} μg/ml, an equivalent anticellular effect requires 10^{-2} μg/ml.

Steliou and coworkers[161,162] tested the myrcene adduct **199**, 1,2-dithiin **234**, and 1,2-dithiane **235** for bioactivity. Compounds **199**, **234**, and **235**, showed no activity against Gram negative bacteria (*E. Coli* and *Ps. aeruginosa*), fungi (*C. albicans*), or mycobacteria (BCG strain of *M. bovis*). However, against Gram positive bacteria (Oxford strain of *Staph. aureus, Staph. epidermis, Strep. pyogenes* and *Strep. faecalis*), disulfides **199**, **234e** and **234f** are active.





234a $R^1 = CH_2CO_2H$; $R^2 = H$
234b $R^1 = CH_2CO_2CH_3$; $R^2 = H$
234c $R^1 = CH_2CO_2CH_3$; $R^2 = H$
234d $R^1 = CH_2CH_2OAc$; $R^2 = H$
234e $R^1 = H$; $R^2 = CH_2CH_2OH$
234f $R^1 = H$; $R^2 = CH_2CH_2OAc$

235a $R = CH_2CO_2H$
235b $R = CH_2CO_2CH_3$
235c $R = CH_2CH_2OH$
235d $R = CH_2CH_2OAc$
235e $R = CH_2CONHCH_2CO_2H$
235f $R = CH_2CONHCH_2CH_3$

In order to test for antiviral activity Steliou and coworkers[161,162] used concentrations of 50 to 100 μM of **199**, **234**, and **235** in DMSO. Table 3 outlines the results observed after two weeks of infecting H9 tissue grown cells (changed twice weekly) with HIV. Compound **234d** was found to be toxic and although none of these compounds showed complete inhibition, compounds **199**, **235a** and **235f** were sufficiently active to warrant further study.

Table 3. Inhibition Studies Against HIV Infection.

Compound	% Infected H9 cells
199	15
234b	95
234d	toxic
235a	20
235b	90
235e	75
235f	30

Since the myrcene adduct **199**, which recorded the best activity against HIV, was also found to induce platelet aggregation, any potential clinical use is negated. The other compounds, however, are completely neutral to platelet aggregation. Interestingly, the activity of compound **235a** against HIV, is lost if methyl esterified (**235b**).

2-Ethenyl-4*H*-1,3-dithiin (**152**) and 3-ethenyl-3,4-dihydro-1,2-dithiin (**153**), which were isolated from caucas, have antithrombotic activity.[101b]

Odorous preparations containing 4-(4-methyl-3-pentenyl)-1,2-dithia-4-cyclohexene (**199**) as an odor enhancing agent have been formulated.[180]

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