THE CHEMISTRY OF 4H-1,3-DITHIINS*

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Abstract——1,2-Dithiins, 1,3-dithiins, 1,4-dithiins, and their derivatives continue to attract considerable attention owing to their bioactivity, to their unique structural features, to their potential superconducting properties, and to their chemical activity. This review describes the preparation, the chemistry, and the biological properties of 4H-1,3-dithiin and its derivatives.

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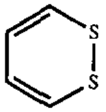
1. INTRODUCTION

1,2-Dithiin (*o*-dithiin, 1,2-dithia-3,5-cyclohexadiene, **1**),[1-3] 4*H*-1,3-dithiin (**2**),[2] 1,4-dithiin (*p*-dithiin, 1,4-dithia-2,5-cyclohexadiene, **3**),[3-5] and their derivatives are found in natural products and are of considerable biological, experimental, and theoretical interest.[6-23] 1,2-Dithiin (**1**), 3,4-dihydro-1,2-dithiin (**4**),[1] and 3,6-dihydro-1,2-dithiin (**5**),[1] and their derivatives are of particular current interest owing to their antiviral properties and to their effectiveness against the acquired immunodeficiency virus (HIV, AIDS).[24,25]



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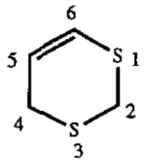

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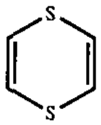

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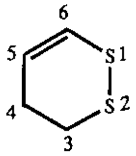

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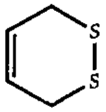

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The major compounds in the young leaves of *Aspilia mossambicesis* and *Aspilia plurisetta* are 3-(5-hexene-1,3-diynyl)-6-(1-propynyl)-1,2-dithiin, thiarubrine A, **6**) and 3-(1,3-pentynyl)-6-(but-1-yn-3-ene)-1,2-dithiin, thiarubrine B, **7**).[26] Thiarubrine A (**6**), thiarubrine B (**7**), and the corresponding thiophene derivatives **8** and **9** are present in the roots of *Chaenactis douglasii* and *Eriophyllum lanatum*.[27-29]

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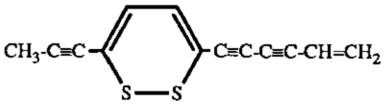
*This paper is dedicated to Professor Sir Derek H.R. Barton on the occasion of his 70th birthday.



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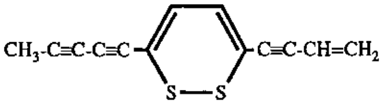

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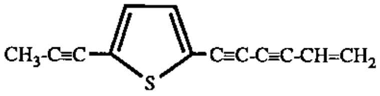

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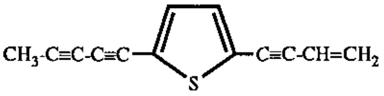

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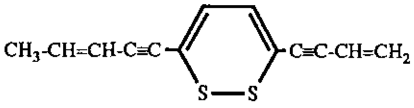
Several red-colored compounds [thiarubrine A (**6**), thiarubrine B (**7**), (E)-3-(3-buten-1-ynyl)-6-(3-penten-1-ynyl)-1,2-dithiin (**10**), (E)-3(3,5-hexadien-1-ynyl)-6-(1-propynyl)-1,2-dithiin (**11**)], and the corresponding thiophene derivatives (**8**, **9**, **12**, **13**) have been isolated from several compositae.[30-42] The occurrence and structure of thiarubrine B (**7**) in *Eriophyllum caespitosum* have been discussed.[37,43-45]



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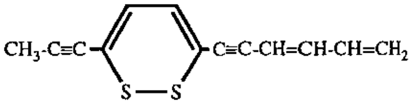

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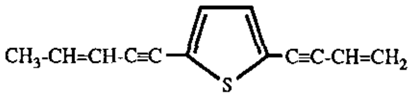

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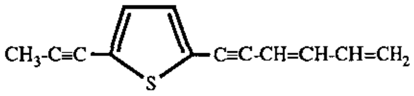

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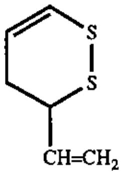
Thiarubrine A (**6**) and/or thiarubrine B (**7**) are also found in roots of *Ambrosia artemisiifolia*,[31] in the aerial parts of *Pegolettia senegalensis*,[32] in *Wedelia hookeriana*,[33] in *Schkuhria multiflora*,[34] in *Verbesina occidentalis*,[35] in roots and overground parts of other *Verbesina species*,[36] and in the roots of *Schkuhria seneciodes*.[45] 3-(3-Buten-1-ynyl)-6-(3-penten-1-ynyl)-1,2-dithiin (**10**) is found in *Picradeniopsis woodhousei*,[38] in the *Lasthenia* species,[39] in *Oyedaea boliviana*,[40] and in *Verbesina*.[41] 3-(3,5-Hexadien-1-ynyl)-6-(1-propynyl)-1,2-dithiin (**11**) has been found in the roots and aerial parts of *Melampodium divaricatum*.[42]

3-Ethenyl-3,4-dihydro-1,2-dithiin (**14**) and 2-ethenyl-4H-1,3-dithiin (**15**) are found in the flavor components of cooked asparagus[46] and 1,2-dithiin (**14**) is a component of garlic.[47-53] Volatile sulfur containing compounds which are enzymically produced from caucas (*A. victorialis*) have been identified.[53] The occurrence of 1-propenyl containing disulfides and 2-methyl-2-pentenal, one of the breakdown products of propanethial S-oxide in caucas, which is one of the garlic like *Allium* species, is chemotaxonomically interesting. 1,2-Dithiin (**14**) and 4H-1,3-dithiin (**15**), which have antithrombotic activity, were isolated from caucas and identified by ir, nmr (2D ^{1}H-^{1}H COSY), and mass spectrometry.[53]



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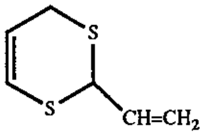

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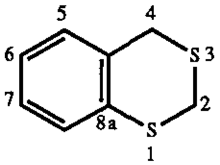
The chemistry of 1,2-dithiins (**1**),[1] 1,4-dithiins (**3**),[4] 3,4-dihydro-1,2-dithiins (**4**),[1] and 3,6-dihydro-1,2-dithiins (**5**)[1] has been recently reviewed. This review, which covers the literature to 1988, will describe the chemistry of 4*H*-1,3-dithiins (**2**),[2] 4*H*-1,3-benzodithiins (**16**),[54] naphtho[1,8-*de*]-1,3-dithiins (**17**),[55] 1,3-dithiino[5,4-*b*]indoles (**18**),[56,57] [1,3]dithiino[5,4-*c*]pyrazoles (**19**),[57,59] 5*H*[1,3]dithiino[4,5-*c*]pyridazines (**20**),[58] 4*H*-1,3-dithiino[5,4-*d*]pyrimidines (**21**),[57,59] 1,2-dithiolo[4,3-*d*]-1,3-dithiin (**22**),[60] and other derivatives of 4*H*-1,3-dithiin (**2**).



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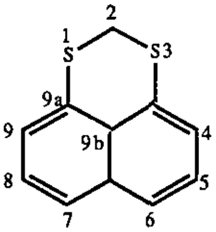

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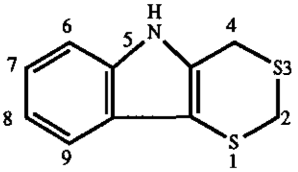

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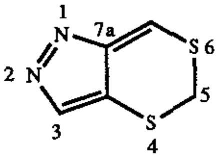

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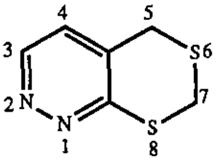

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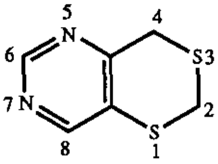

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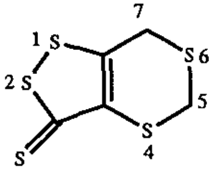

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2. 4*H*-1,3-DITHIINS

2.1 Structure

Preliminary *ab initio* molecular orbital calculations show that the nonplanar conformational isomers of 4*H*-1,3-dithiin (**2**), 3,4-dihydro-1,2-dithiin (**4**), and 3,6-dihydro-1,2-dithiin (**5**) are more stable than the corresponding planar isomers (Tables 1, 2, 3)[1,6,7] A comparison of Tables 1 and 2 shows that 3,4-dihydro-1,2-dithiin (**4**) is more stable than 4*H*-1,3-dithiin (**2**).

Table 1. *Ab Initio* Molecular Orbital Calculations for 4H-1,3-Dithiin (**2**)

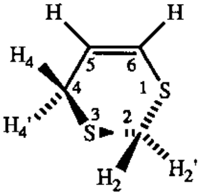
		conformation	
		planar	nonplanar
		C_s	C_1
total energy (au) at RHF/3-21G$^{(*)}$		-945.39667	-945.414241
energy difference (kJ mol^{-1})		41.34	
total energy (au) at MP2/6-31G*//RHF/3-21G$^{(*)}$			
energy difference (kJ mol^{-1})			
r_{S1C2}	Å	1.820	1.812
r_{C2S3}	Å	1.829	1.810
r_{S3C4}	Å	1.828	1.816
r_{C4C5}	Å	1.501	1.512
r_{C5C6}	Å	1.313	1.318
r_{C6S1}	Å	1.746	1.756
r_{C2H2}	Å	1.079	1.080
$r_{C2H2'}$	Å	1.079	1.081
r_{C4H4}	Å	1.083	1.084
$r_{C4H4'}$	Å	1.083	1.083
r_{C5H5}	Å	1.075	1.075
r_{C6H6}	Å	1.074	1.074
<S1C2S3		122.110	114.090
<C2S3C4		109.910	97.230
<S3C4C5		120.190	114.740
<C4C5C6		129.520	127.730
<C5C6S1		131.280	129.180
<C6S1C2		106.990	101.190
<H2C2H2'		108.580	108.430
<H4C4H4'		107.400	107.220
<H5C5C6		117.480	117.680
<H6C6C5		118.980	119.340
<S1C2S3C4		0	65.890
<C2S3C4C5		0	52.450
<S3C4C5C6		0	24.240
<C4C5C6S1		0	1.040
<C5C6S1C2		0	9.660
<C6S1C2S3		0	46.580

Table 2. *Ab Initio* Molecular Orbital Calculations for 3,4-Dihydro-1,2-dithiin (**4**)

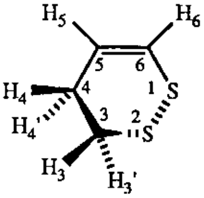
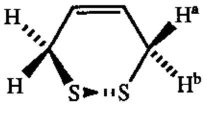
		conformation	
		planar C_s	nonplanar C_1
total energy (au) at RHF/3-21G(*)		-945.39329	-945.4175
energy difference (kJ mol^{-1})		63.60	
at MP2/6-31G*//RHF/3-21G(*) energy difference (kJ mol^{-1})			
r_{S1S2}	Å	2.082	2.055
r_{S2C3}	Å	1.840	1.822
r_{C3C4}	Å	1.556	1.538
r_{C4C5}	Å	1.505	1.515
r_{C5C6}	Å	1.313	1.318
r_{C6S1}	Å	1.744	1.766
r_{C3H3}	Å	1.079	1.082
$r_{C3H3'}$	Å	1.079	1.081
r_{C4H4}	Å	1.085	1.085
$r_{C4H4'}$	Å	1.085	1.087
r_{C5H5}	Å	1.075	1.075
r_{C6H6}	Å	1.075	1.073
<S1C2S3		109.470	97.440
<S2C3C4		122.450	111.130
<C3C4C5		121.050	115.250
<C4C5C6		130.320	128.210
<C5C6S1		130.770	127.450
<C6S1S2		105.940	100.740
<H3C3H3'		107.910	108.710
<H4C4H4'		106.030	107.040
<H5C5C6		116.750	117.300
<H6C6C5		119.410	120.120
<S1S2C3C4		0	69.350
<S2C3C4C5		0	52.330
<C3C4C5C6		0	12.100
<C4C5C6S1		0	0.220
<C5C6S1S2		0	23.200
<C6S1S2C3		0	50.050

Table 3. *Ab Initio* Molecular Orbital Calculations for 3,4-Dihydro-1,2-dithiin (**4**)

 7		conformation	
		planar C_{2v}	nonplanar C_2
total energy (au) 3-21G*		-945.39189	-945.41604
energy difference between C_{2v} and C_2 (kJ mol^{-1})		63.40	
(kJ mol^{-1})			-950.75680
total energy (au) MP2 6-31G*			
energy difference between C_{2v} and C_2 (kJ mol^{-1})			
$r_{S\text{-}S}$	Å	2.097	2.049
$r_{C\text{-}S}$	Å	1.826	1.818
$r_{C\text{-}C}$	Å	1.503	1.515
$r_{C=C}$	Å	1.312	1.317
$r_{C\text{-}H^a}$	Å	1.083	1.083
$r_{C\text{-}H^b}$	Å	—	1.084
$r_{=C\text{-}H}$	Å	1.076	1.075
<H-C-H		107.610	107.920
<H-C=C		117.450	118.270
<C-S-S		108.830	97.890
<C-C=C		130.780	127.790
<C-C-S		120.390	114.140
dihedral angle CSSC		0	63.390
dihedral angle CCSS		0	52.570
dihedral angle CCCS		0	21.120
CCCC		0	0.710
twist angle[a]		0	36.860

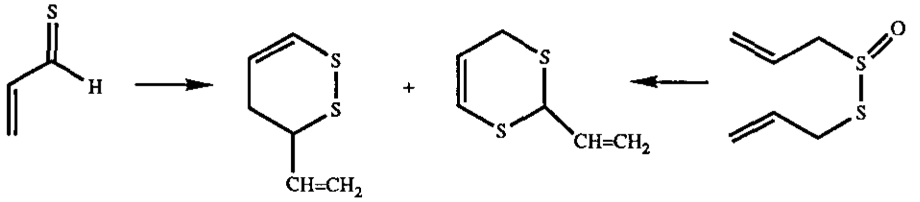
a) The twist angle between the S-S bond and the plane involving the four carbon atoms.

2.2 Preparation

4H-1,3-Dithiin (**2**) has been reported as a product from the photoreduction of benzophenone by 1,3-dithiane.[61a]

Thiocarbonyl compounds, with the carbon-sulfur double bond serving as the 2π dienophile component, have been employed in Diels-Alder reactions ([4 + 2] cycloadditions) to prepare thiopyranyl systems.[61b] However, dithioesters, thioaldehydes, and thioketones may participate as the diene partners of Diels-Alder reactions in which the thiocarbonyl group comprises a component of the 4π diene system.[61-68]

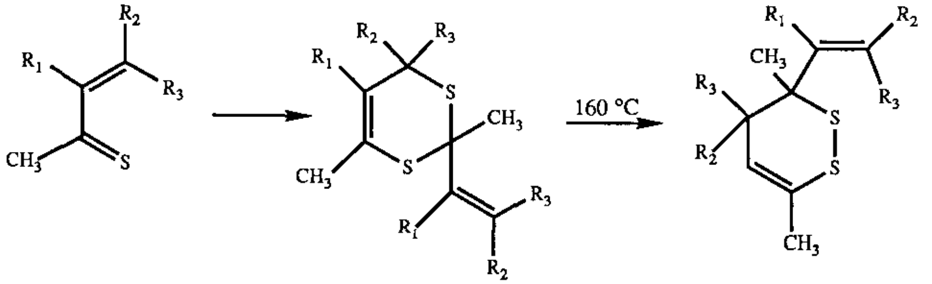
Dially disulfide decomposed quantitatively at 660 °K in the gas phase to give an equimolar mixture of propene and 2-propenethial.[61c] On cool-trapping, 2-propenethial dimerized and the Diels-Adler adduct, predominantly the kinetic product 2-ethenyl-4H-1,3-dithiin (**15**), was isolated together with 3-ethenyl-3,4-dihydro-1,2-dithiin (**14**).[61c,61d,62] Treating propenal with hydrogen sulfide and ethyl orthoformate in the presence of zinc chloride gave 1,2-dithiin **14** and 1,3-dithiin **15**.[63] S-3-Propenyl 2-propenethiosulfinate (allicin), which undergoes β-elimination to afford 2-propenesulfinic acid and 2-propenethial, is a precursor of 1,2-dithiin (**14**) and 1,3-dithiin (**15**) (eq. 1).[47] The formation of 1,2-dithiin (**14**) in the aromatic components of cooked asparagus is assumed to involve reaction of hydrogen sulfide with 2-propenethial[63] which results from the thermal degradation of methionine.



(1)

14 15

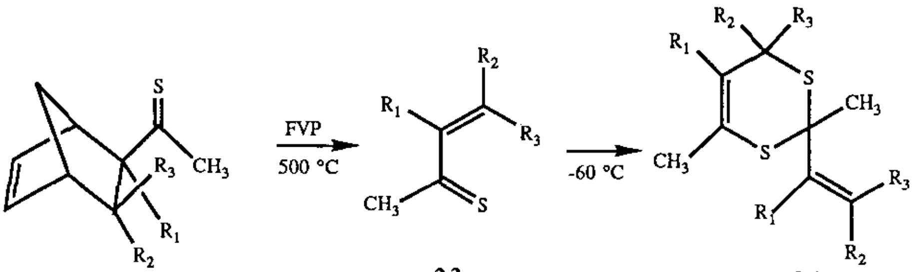
Aliphatic α,β-unsaturated thioketones are unstable at 20 to 25 °C and exist in the dimeric 4H-1,3-dithiin structure (**24**) or the 1,2-dithiin structure (**25**) (eq. 2).[64-68] Flash vacuum pyrolysis (FVP) preparation of α,β-unsaturated thioketones also led to regiospecific Diels-Alder dimerization with 4π and 2π thiocarbonyl participation (eq. 3). Molecular orbital calculations of the cyclodimerization have been reported.[64b]



(2)

23a $R_1 = R_2 = R_3 = H$
23b $R_1 = R_3 = H,\ R_2 = CH_3$
23c $R_1 = CH_3, R_2 = R_3 = H$
23d $R_1 = H,\ R_2 = R_3 = CH_3$

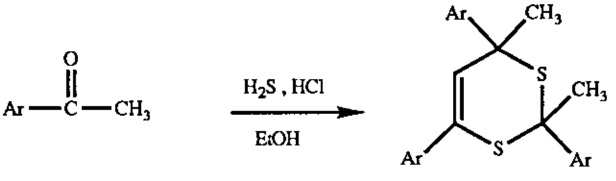
24 **25**



(3)

23 **24**

There is a need for careful investigations in order to accurately interpret the preferred kinetic mode and regioselectivity of the Diels-Alder dimerization reactions of α,β-unsaturated thioaldehydes and thioketones owing to the reversible nature of the cycloadditions and to the potential participation of the products in subsequent rearrangements. Substituted aryl ethanones react with hydrochloric acid and hydrogen sulfide to give 2,4-dimethyl-2,4,6-triaryl-4*H*-1,3-dithiins (**26**) (eq. 4).[69-72] 1-(4-Methoxyphenyl)-1-propanone reacts similarly.[73]



(4)

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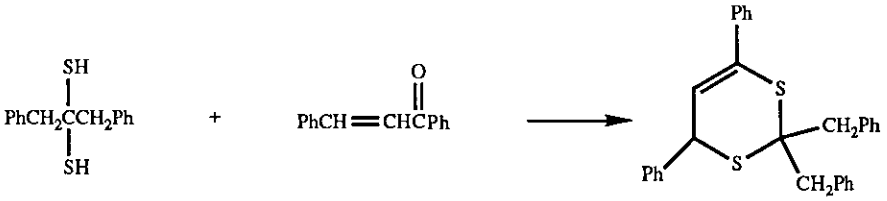
2,2-Dibenzyl-4,6-diphenyl-4*H*-1,3-dithiin (**29**) was isolated from the reaction of 1,3-diphenylpropane-2,2-dithiol (**27**) with benzalacetophenone (chalcone, **28**) in ethanolic hydrogen chloride (eq. 5,6).[74-76] Other examples of 4*H*-1,3-dithiins from α,β-unsaturated carbonyl compounds are shown in equations 6 and 7.[71]



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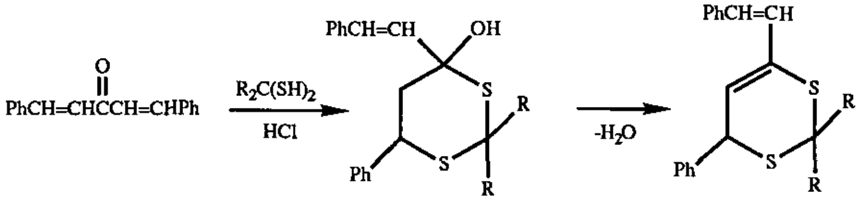
27 **28** **29**

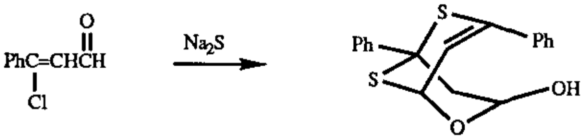


(6)

30 **31**

32a R = CH_3
32b R = C_2H_5
32c R = $(CH_2)_5$

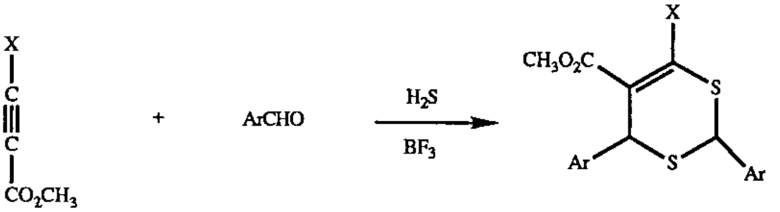
Attempts to prepare β-mercaptocinnamaldehyde from β-chlorocinnamaldehyde (**33**) and sodium sulfide led to a dimer (bicyclo[3.3.1]-5,7-diphenyl-3-hydroxy-2-oxa-6,9-dithia-7-nonene, **34**).[77]



(7)

33 **34**

A series of 4*H*-1,3-dithiins (**35**) has been prepared by reaction of an alkynyl ester and an aromatic aldehyde with hydrogen sulfide in the presence of boron trifluoride.[78]

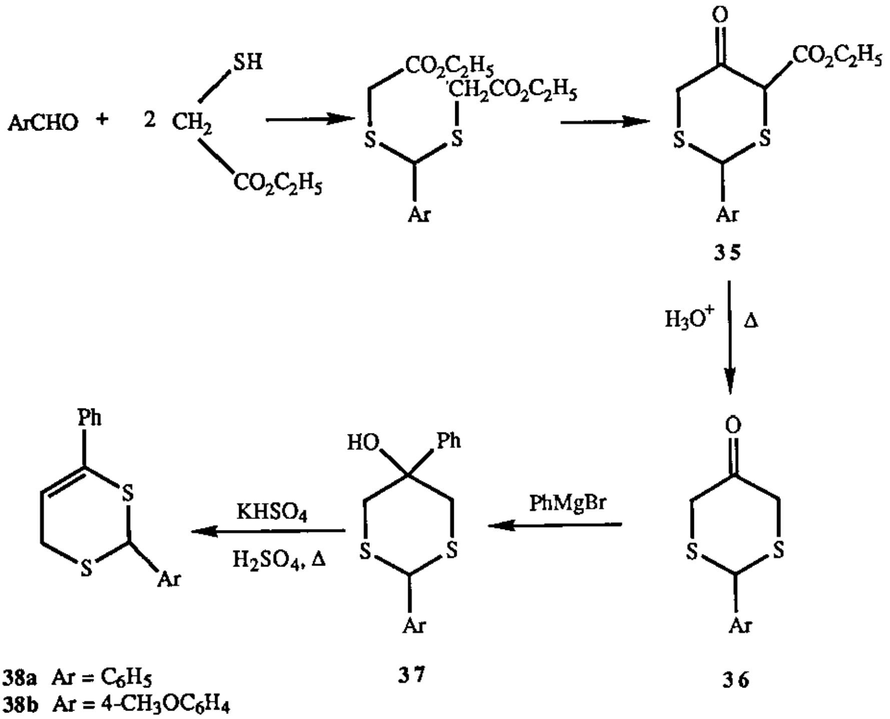


(8)

35a X = H, Ar = C_6H_5
35b X = H, Ar = 4-$CH_3C_6H_4$
35c X = H, Ar = 4-ClC_6H_4
35d X = CO_2CH_3, Ar = C_6H_5

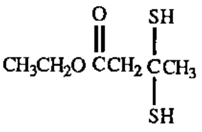
Scheme I shows the first general synthesis of 4*H*-1,3-dithiins (**38**).[60,79]

Scheme I



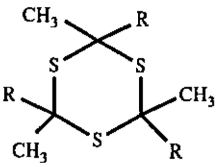
38a Ar = C_6H_5
38b Ar = 4-$CH_3OC_6H_4$

Ethyl 3-oxobutanoate reacts with hydrogen chloride and hydrogen sulfide to give products **39a**, **39b**, and 2,6-dimethyl-2-ethoxycarbonylmethyl-4-oxo-1,3-dithiin (**40**).[80] A mechanism for the formation of **40** *via* the dimerization of **39** and subsequent elimination of ethanol was proposed.[80]

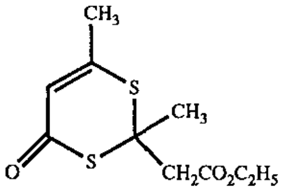


$CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_2\underset{SH}{\overset{SH}{C}}CH_3$

39a

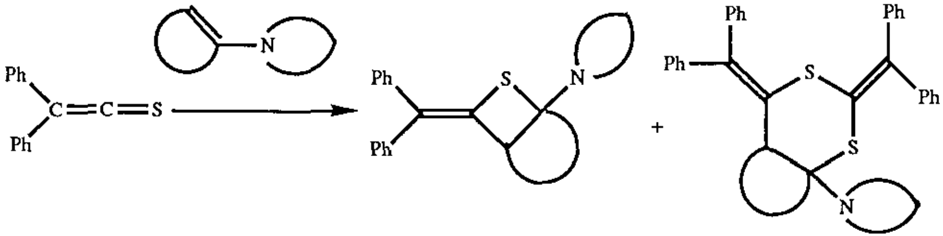


39b $R = CH_2CO_2C_2H_5$

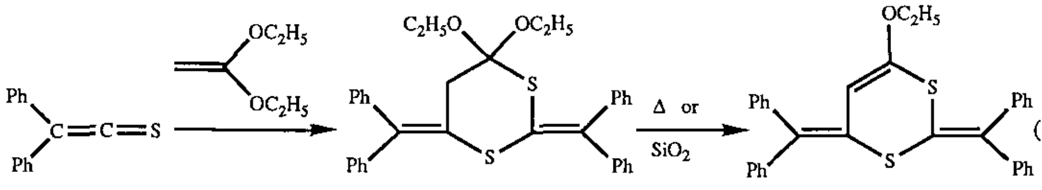


40

Diphenylthioketene (**41**)[81] gives [2 + 2] cycloaddition products with electron rich unsaturated systems such as enamines and ketene acetals (eq. 9, 10).[82,83] A mechanism *via* a zwitterionic intermediate is suggested by the formation of 2:1 cycloadducts.

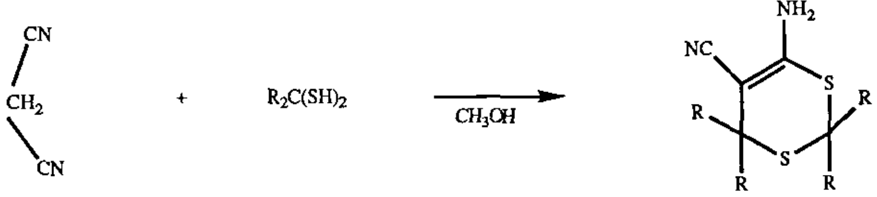


41 **42** **43** (9)



41 **44** **45** (10)

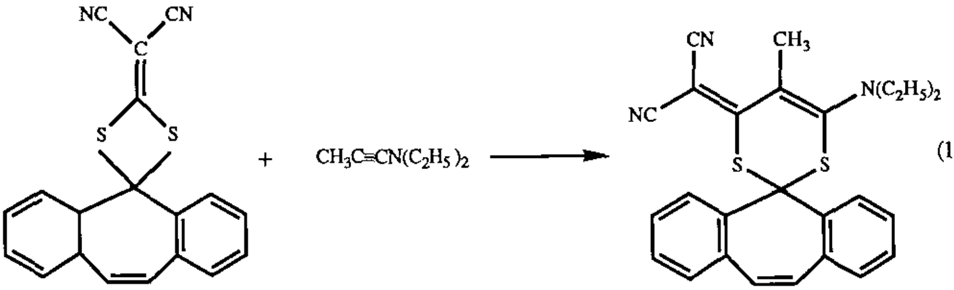
Dicyanomethane (malononitrile)[84-88] reacts with *gem*-dithiols in the presence of potassium hydroxide to give 4*H*-1,3-dithiins (**46**).[89] Benzylidenemalononitrile and cyclohexylidenemalononitrile gave analogous 4*H*-1,3-dithiins.



(11)

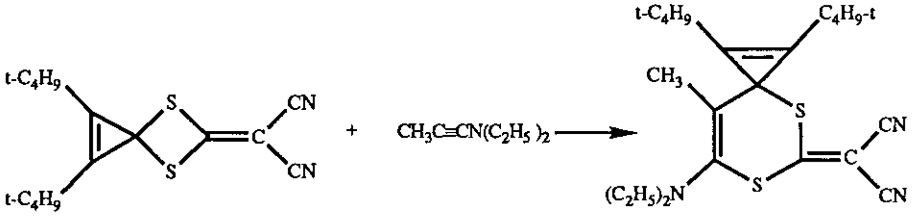
46a $R = CH_3$
46b $R = -(CH_2)_4-$
46c $R = -(CH_2)_5-$

The 2,4-bis(methylene)-1,3-dithietane (**47**) reacts with 1-(*N*,*N*-diethylamino)propyne (**48**) to yield **49**.[90] The reaction of spiro derivative **50** with **48** to give **51** may proceed via a cyclopropenium cation.[106]



(12)

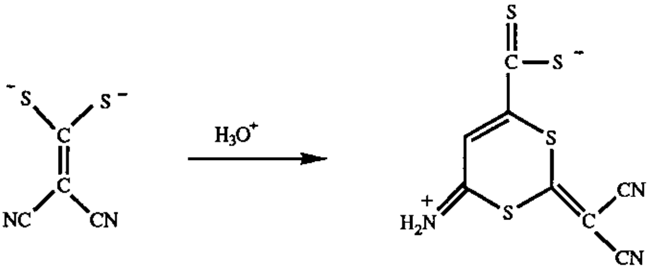
47 **48** **49**



(13)

50 **48** **51**

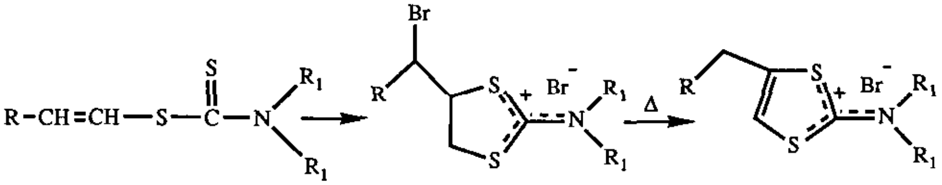
The substituted 4*H*-1,3-dithiin **53** is prepared from salt 52.[91]



(14)

52 **53**

Bromination of β,γ-unsaturated dithiocarbamates (**54**) leads to the quantitative formation of the corresponding 2-dialkylamino-4-(α-bromoalkyl)-1,3-dithioanylium bromides (**55**) *via* regiospecific (S-5) participation by the dithiocarbamate function.[92] Thermal transformation of **55** into 2-dialkylamino-4-alkyl-1,3-dithiolium salts (**56**) occurs in good yields.[93] The dithiolium salts (**56**) an important class of synthetic intermediates[94] for the preparation of tetrathiofuvalene derivatives which possess interesting electroconductivity properties.[95] This new synthetic route to 4-alkyl-1,3-dithiolium salts is more advantageous than other methods[96,97] owing to its operational simplicity and to the accessibility of starting materials.

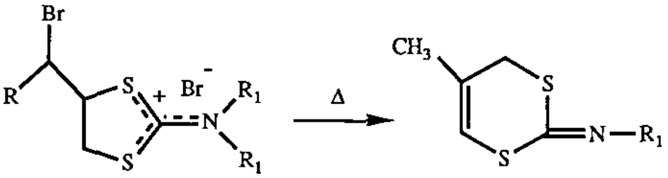


(15)

54 **55**

56a $R = H_1, R_1 = CH_3$
56a $R = H_1, R_1 = C_2H_5$
56c $R = R_1 = CH_3$

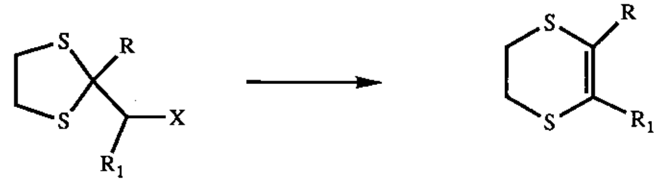
Pyrolysis of 2-dialkylamino-4-bromomethyl-4-methyl-1,3-dithioanylium bromides (**55**, $R = R_1 = CH_3$; $R = CH_3$; $R = CH_3$, $R_1 = C_2H_5$) gives the six-membered 2-alkyl-imino-5-methyl-1,3-dithia-4-cyclohexenes (2-alkylimino-5-methyl-1,3-dithiins, **57**).[98] This novel ring transformation may be the first example of a ring expansion of 1,3-dithiolane derivatives into a 1,3-dithiin system, although ring expansions of 1,3-dithiolane derivatives such as **58** into dihydro-1,4-dithiin systems (**59**) is well precedented.[99-103] A crucial step in the synthesis of the antibiotic holomycin (**61**) is the ring contraction of a 1,3-dithiin (**60**) to a 1,2-dithiole (eq. 18).[104,105]



(16)

55

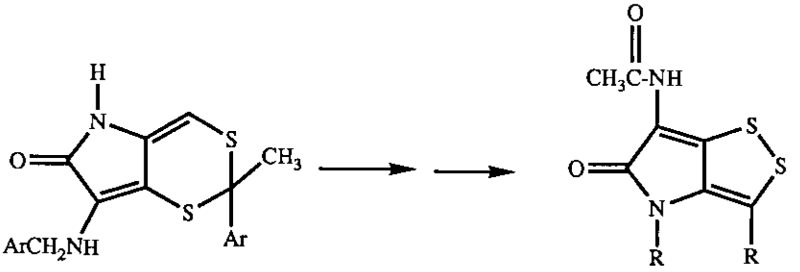
57a $R_1 = CH_3$
57b $R_1 = C_2H_5$



(17)

58 X = OAc, Br, Cl

59

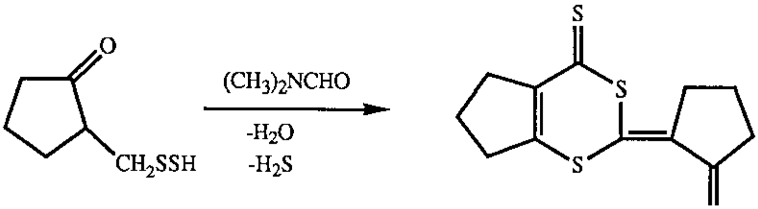


(18)

60

61a R = H
61b R = CO_2H

In dipolar aprotic solvents, 2-oxocyclopentanedithiocarboxylic acid (**62**) is converted into 6,7-dihydro-2-(2-oxocyclopentylidene)cyclopenta[*d*][1,3] dithiin-4(5*H*)-thione **63** or into its positional isomer.[106]

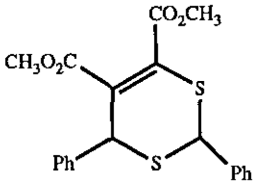


(19)

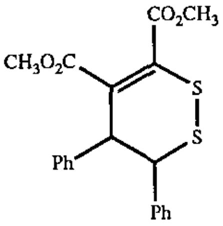
62

63

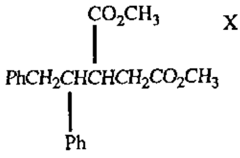
Thermolysis (185 °C) of dimethyl 2,4-diphenyl-1,3-dithiin-5,6-dicarboxylate (**35d**) affords isomeric dimethyl 3,4-dihydro-3,4-diphenyl-1,2-dithiin-5,6-dicarboxylate (**64**).[78] Desulfurization of **64** with Raney nickel gave diester (**65**). The mechanism of this unusual rearrangement might involve fission of a C-S bond with formation of intermediate allylic (and benzylic) diradicals (Scheme II). The structures of the 1,3-dithiins **35** were further supported by their spectral properties and oxidative rearrangement to the dithiolium salts (**66**).[78]



35d

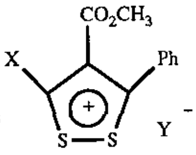


64



$$PhCH_2\underset{Ph}{CH}\overset{CO_2CH_3}{CH}CH_2CO_2CH_3$$

65



66

X = H or CO_2CH_3

Y^- = Br or ClO_4

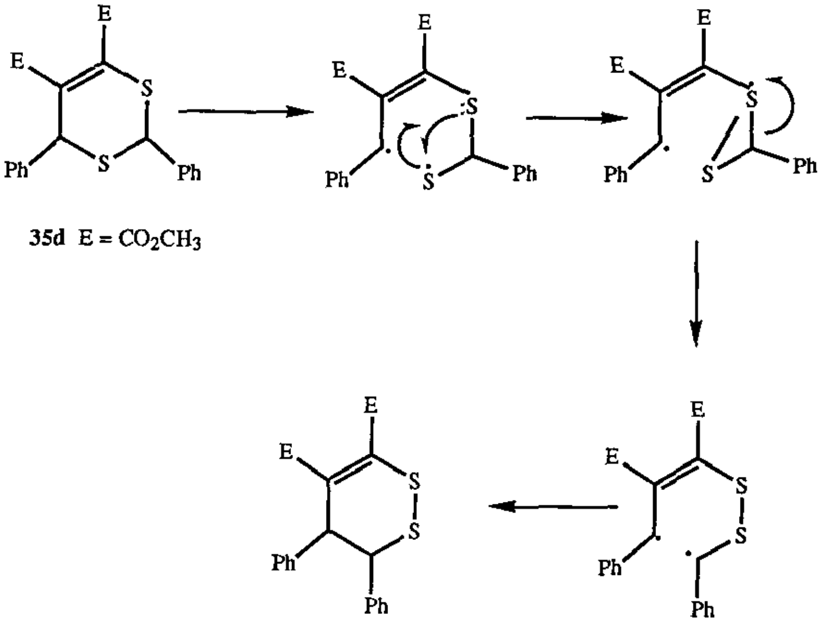
2.3 REACTIONS

The unexplored chemistry of 4H-1,3-dithiin (**2**) and its derivatives remains a fertile area for future study.

The isomerization of 2-ethenyl-4H-1,3-dithiin (**15**) to 3-ethenyl-3,4-dihydro-1,2-dithiin (**14**) has been observed (eq. 1).[61-63]

4H-1,3-Dithiins (**38**, Scheme I) react with dibromine in ethanoic acid to give aldehydes (**68**, 55-60%) and 4-phenyl-1,2-dithiolium bromide (**71**, Scheme III).[79] Sulfuryl chloride reacts similarly with **38**.

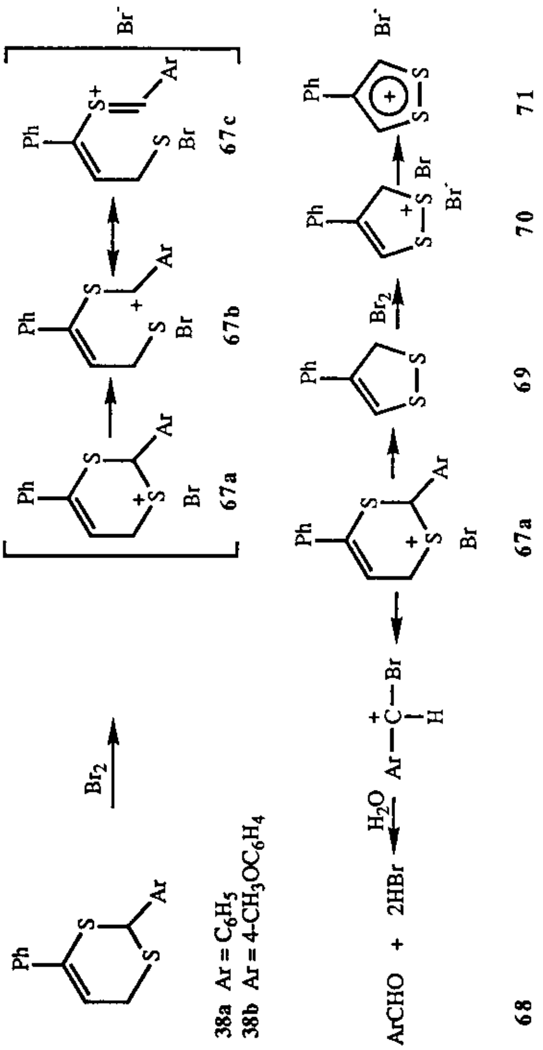
Scheme II



35d $E = CO_2CH_3$

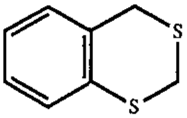
64

Scheme III

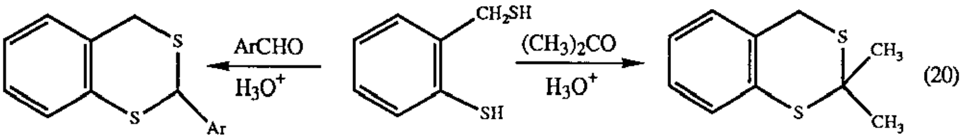

Ph
Ar
38a Ar = C6H5
38b Ar = 4-CH3OC6H4
Br2
67a
67b
67c
Br
Br⁻
ArCHO + 2HBr
H2O
68
69
70
71

Some of the versatile chemical reactivity of the labile 4H-1,3-dithiin **53** (eq. 13) is shown in Scheme IV.[91] It is seen that a 1,2-dithiolethione (**72**), an isothiazole (**73**), and open chain products (**74**, **75**) are formed.

3. 4H-BENZO-1,3-DITHIINS

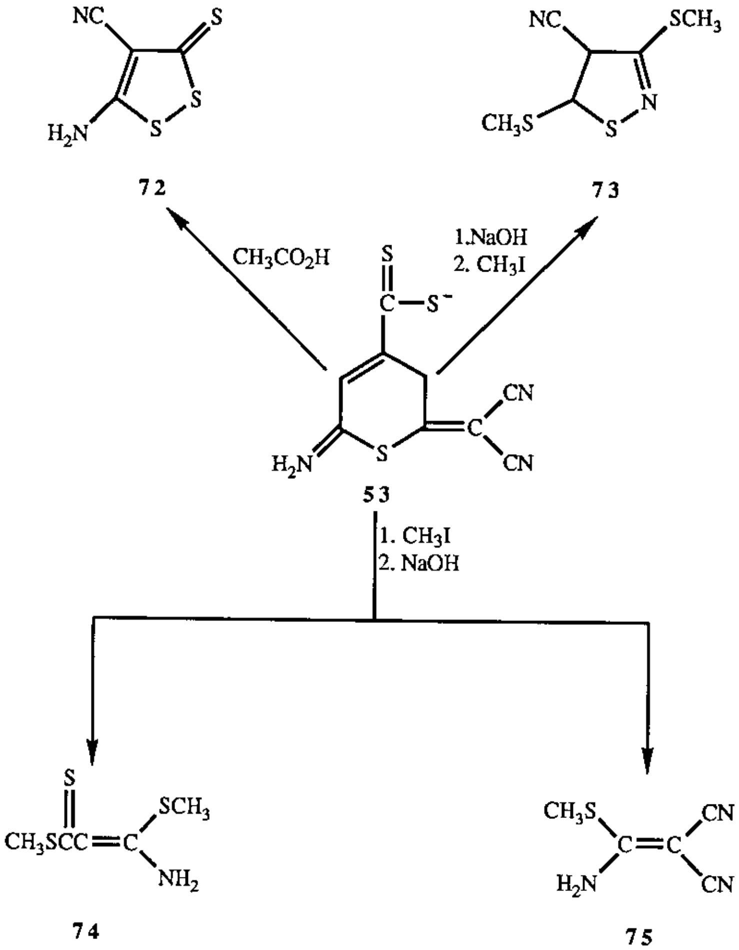

16

Although the parent compound (4H-benzo-1,3-dithiin, **16**) is not known, 2-aryl-4H-1,3-benzodithiins (**77**) and 2,2-dimethyl-4H-1,3-benzodithiin (**78**) have been prepared from 1-mercapto-2-thiomethylbenzene (**76**).[54,79] Permanganate ion oxidizes the 1,3-dithiin (**78**) to the corresponding disulfone(**79**).

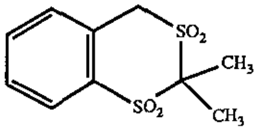


77 **76** **78**

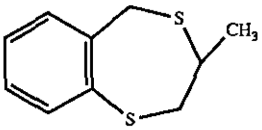
Scheme IV



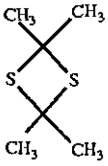
Photolysis of the 1,3-dithiin (**78**) gave the rearranged product (**80**) (15%) in addition to compound (**81**) (4%) and disulfide (**82**) (3%).[107] The absence of compound (**83**) suggests that initial carbon-sulfur bond cleavage occurs only in the direction to give the more stable thiyl radical **84a**.



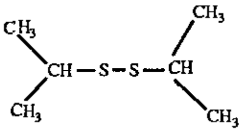
79

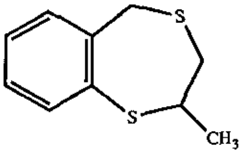


80



81





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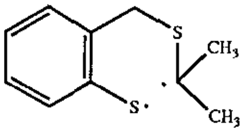
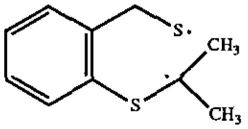
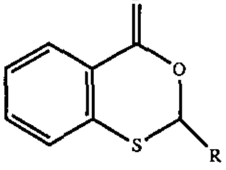


84a

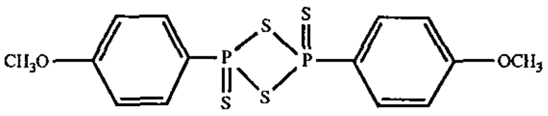


84b

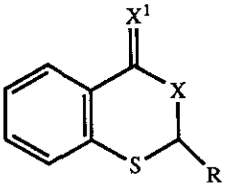
3,1-Benzoxathian-4-ones (**85**), when heated with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson reagent, **86**) or with P_4S_{10} gave one or more of the following products: 3,1-benzoxathian-4-thione (**87**), 1,3-benzothian-4-one (**88**), 1,3-benzodithian-4-thione (**89**), and 3*H*-1,2-benzodithiole-3-thione (**90**).[108] Lithium aluminum hydride reduces thione (**90**) to dithiol (**76**).[73]



85a R = H
85b R = CCl_3
85c R = C_6H_5
85d R = 2-nitrophenyl



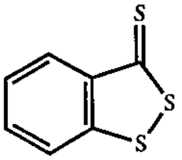
86



87 $X^1 = S$, $X = O$

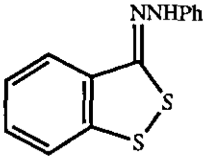
88 $X^1 = O$, $X = S$

89 $X^1 = S$, $X = S$

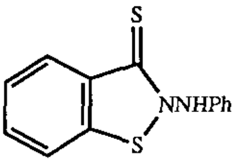


90

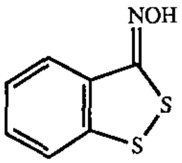
Compound **89** (R = Ph) reacted with phenylhydrazine or hydroxylamine to give known compounds **91** and **92**, respectively.[108] 4-Phenylhydrazono-2-phenyl-1,3-benzodithian (**93**) was isolated as a byproduct from the phenylhydrazine reaction. The 3*H*-1,2-benzodithiol-3-imines (*eg.* **91a**) are in equilibrium (Dimroth rearrangement) with 1,2-benzisothiazole-3(2*H*)-thiones (*eg.* **91b**).[108]



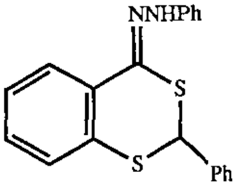
91a



91b

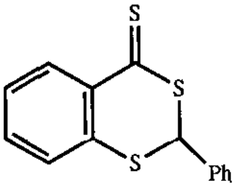


92

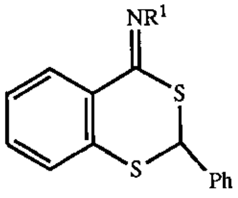


93

Another report[109] describes the reaction of 3,1-benzoxathian-4-ones (**85**, R = $(CH_2)_{10}CH_3$, CH_3, Ph) with Lawesson reagent (**86**) or with P_4S_{10} to give a mixture of **87**, **89**, and 1,2-benzodithiolethione (**90**). Compound **89** ($X = X^1 = S$; R = Ph) reacts with primary amines and hydrazines to give **94** ($X = S$; $X^1 = NR^1$; R^1 = alkyl, aryl). The reactions of **89** with Ph_2CN_2, diazofluorene, and Cu-bronze have also been studied.[109]

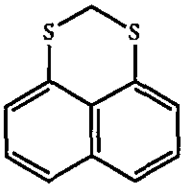


89



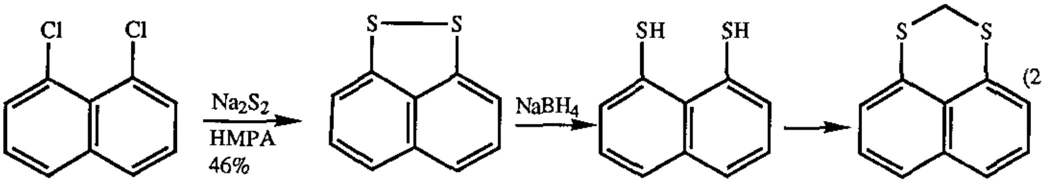
94

4. NAPHTHO[1,8-*de*]-1,3-DITHIINS



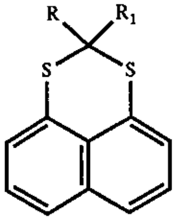
17

Naphtho[1,8-*de*]-1,3-dithiin (**17**)[55,110] was prepared in 26% yield by treatment of 1,8-dimercaptonaphthalene (naphtho[1,8-*cd*]-1,2-dithiole, **97**) with sodium hydride and diiodomethane at 22-24 °C in tetrahydrofuran.

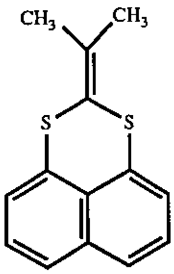


95 **96** **97** **17** (21)

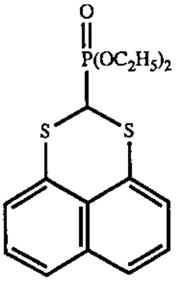
The reaction of dithiol (**97**) with propanone afforded the 1,3-dithiin (**98**).[111] 2-Phenylnaphtho[1,8-*de*]-1,3-dithiin (**99**) was prepared from the reaction of the dithiol (**97**) and phenylmethanal.[112] Naphtho[1,8-*de*]-2-isopropylidene-1,3-dithiin (**100**) was prepared (95%) from the Wadsworth-Emmons reaction of diethyl [naphtho[1,8-de]-1,3-diin-2-yl]phosphonate (**101**) and propanone.[55] Compound **101** was prepared from naphtho[1,8-*de*]-1,3-dithiin-2-thione (**102**) (eq. 22).[55]



98 R = R^1 = CH_3
99 R = H, R^1 = C_6H_5



100



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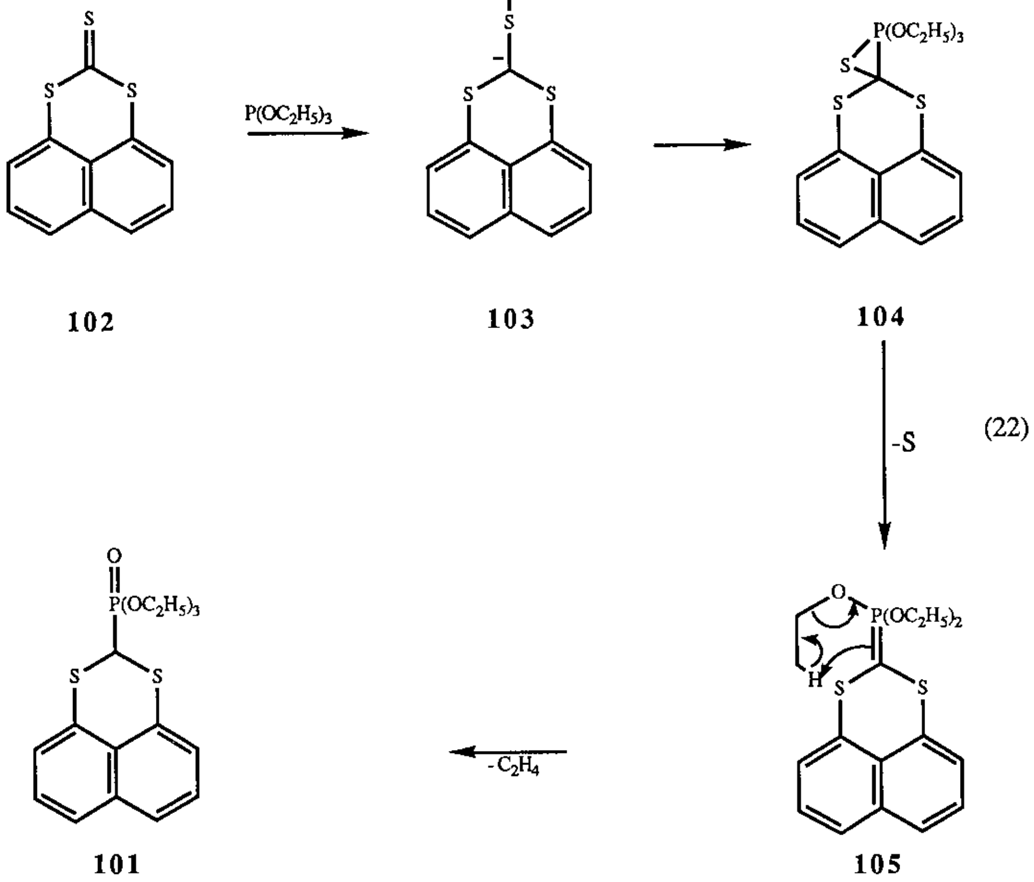
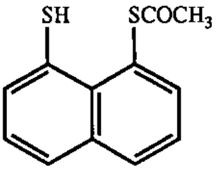


(22)

The tetrahedral intermediate (**107**) in the intramolecular acyl transfer reaction of mono-S-acylated 1,8-naphthalenedithiol (**106**) was found to be sufficiently stable to allow isolation or direct characterization by spectroscopy.[113] Compound **107** (**106**) dissolves in 96% sulfuric acid to give an intense blush-violet solution showing a single methyl signal at δ 2.75 (ppm from external TMS) and a multiplet at δ 7.0 - 8.0. Dilution of the solution with cold water gave a trace of **107** (**106**) and compound **108**. A carbenium ion intermediate was proposed.[113]



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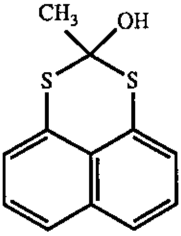
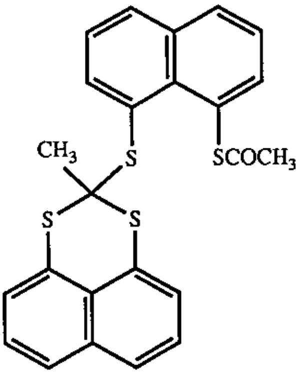
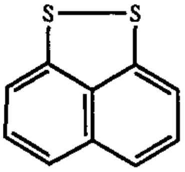


107

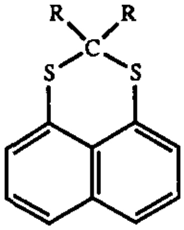


108

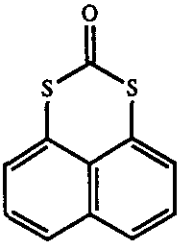
Refluxing 1,2-dithaacenenaphthene (**96**) and bis(toluenesulfonyl)diazomethane with copper acetylacetonate in benzene gave the insertion product (**109**) (88%).[114] The pyrolysis of **109** or **110** at 148 °C gave carbonyl compound (**111**). Similar reactions were observed with **111** and diphenyldiazomethane in the presence of copper salts. The fact that diphenyl disulfide did not react with these carbenes implied that the five membered ring disulfide was more reactive to electrophilic reagents than ordinary sulfides.[114]



96

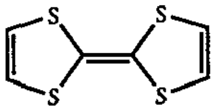


109 R = 4-$CH_3C_6H_4$
110 R = C_6H_5



111

The discovery of tetrathiafulvalene (TTF, **112**) forming charge-transfer salts with low-dimensionally metallic properties has generated considerable interest in other electron donors which exhibit similar conductivity.55 Binaphtho[1,8-de]-1,3-dithiin-2-ylidene (**113**), which belongs to the same tetrathiaethylene class, but differs structurally from TTF (**112**) in the fused heterocyclic member, was prepared and its donor character was examined by cyclic voltammetry.[55,110]



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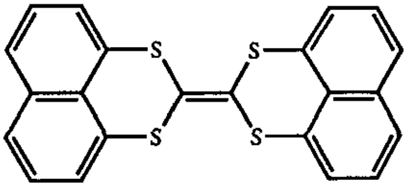
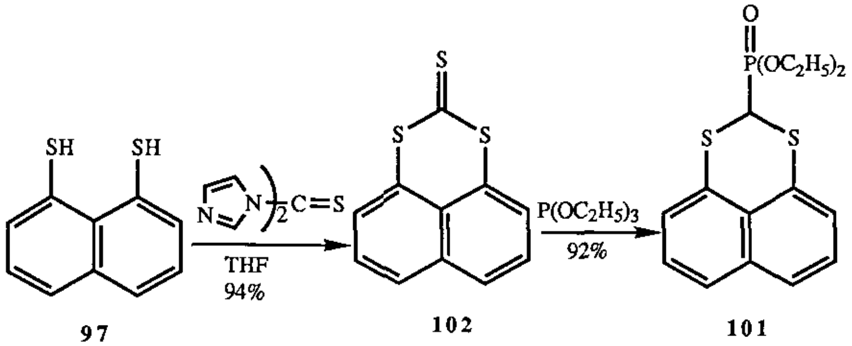
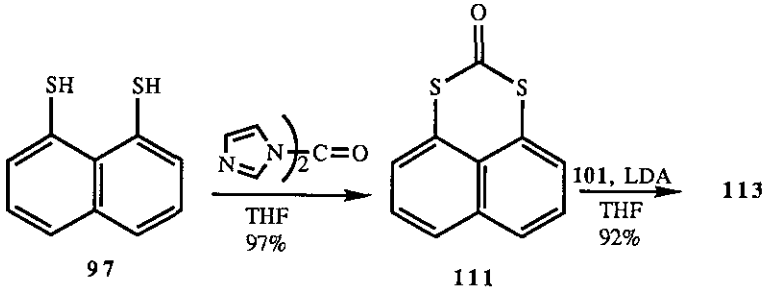


113



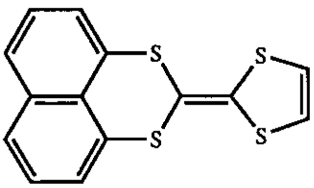
(23)

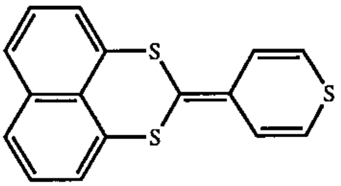


(24)

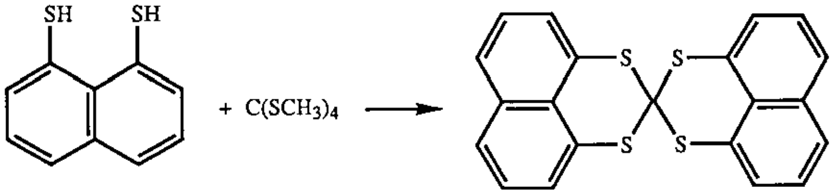
The cyclic voltammetry of **113** exhibited a reversible redox wave, whose half-wave oxidation potential was situated at 1.14 V vs. a Ag/AgCl reference electrode in cyanobenzene (0.1 M $(C_4H_9)_4NClO_4$, Pt electrode, 100 mV·s^{-1} scan rate).[55] In contrast, the cyclic voltammetry of **17** and **105** showed irreversible oxidations with somewhat higher peak potentials. The easier oxidation of **113** and the greater stability of the resulting radical cation may be attributed to the extended conjugation of π electrons through the central olefin.[55]

Although cyclic voltammetry indicated that symmetrical 2,2'-binaphtho[1,8-*de*]-1,3-dithiinylidene (**113**) and its selenium analog were poor donors, unsymmetrical 2-(1,3-dithio-2-ylidene)naphtho[1,8-de]-1,3-dithiin (**114**) and 2-(4H-thiopyran-4-ylidine)naphtho[1,8-*de*]1,3-dithiin (**115**) possess considerable donor abilities.[111] These compounds (**114**, **115**) are capable of forming crystalline charge transfer complexes with strong acceptors as TCNQ, TCNQF$_4$, and DDQ, which are semiconducting.[55]


114


115

Nonplanar 2,2'-spirobinaphtho[1,8-de]-1,3-dithiin (**111**) has been prepared from the dithiol (**97**) and tetramethyl orthothiocarbonate (**116**).[111] The He(I) PE spectra of **98** and **117** have been measured.[111]

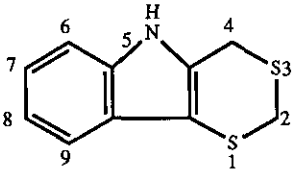


(25)

116 **117**

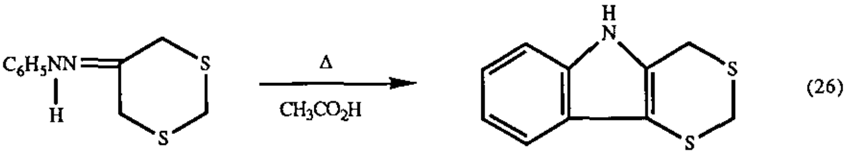
The He(I) photoelectron spectra of naphtho[1,8-*de*]-1,3-dithiin (**17**) has also been measured.[115] Oxidation of **17** gives the radical cation. The PES ionization energies and the esr coupling in the radical cation were satisfactorily reproduced by a molecular state parameterized HMO model.[115]

5. 1,3-DITHIINO[5,4-*b*]INDOLES



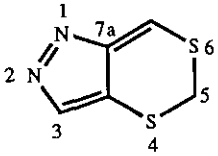
18

The 4,5-dihydro derivative **18** was obtained from 1,3-dithiane-5-phenylhydrazone (**118**).[56,57]



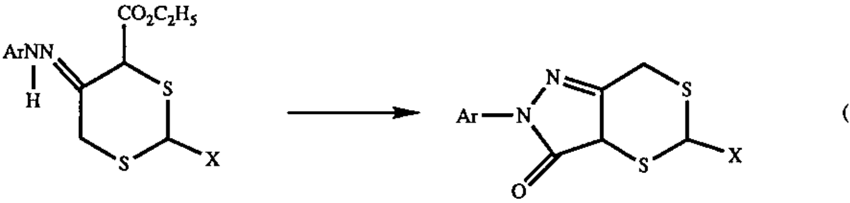
118 **18**

6. [1,3]DITHIINO[5,4-*c*]PYRAZOLES



19

The hydrazones of 2,7-dihydro-1,3-dithiino[5,4-*c*]-pyrazol-3(3*a*H)-ones were prepared from ethyl 5-oxo-1,3-dithiane-4-carboxylates (**119**).[57,59]



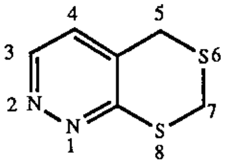
119

(27)

	Ar	X
120a	H	H
120b	H	4-ClC_6H_4
120c	C_6H_5	H
120d	C_6H_5	CH3
120e	4-$HO_3SC_6H_4$	CH_3
120f	C_6H_5	-$(CH_2)_5$-

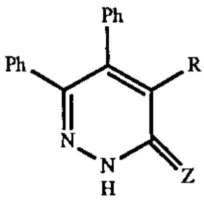
The acetamide derivative of [1,3]dithiino[5,4-*c*]pyrazole (**19**) and 2,7-dihydro-5-phenyl[1,3]dithiino[5,4-*c*]pyrazole-(3*a*H)-one were prepared and tested as sensitive silver halide photothermographic materials for producing dye images.[116]

7. 5H-[1,3]DITHIINO[4,5-*c*]PYRIDAZINE

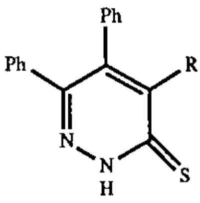


20

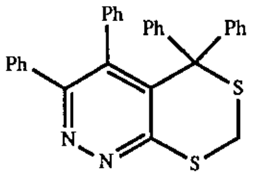
Reaction of **121** (R = CPh_2OH; Z = O,S) with P_4S_{10} gave **122** (R = CPh_2SH; Z = S) which undergoes cyclocondensation with dimethoxymethane to give 3,4,5,5-tetraphenyl-5H-[1,3]dithiino[4,5-*c*]pyridazine (**123**, 66%),[58] which is a representative of a new ring system (1,3-dithiano-[4,5-*c*]pyridazine).[117]



121

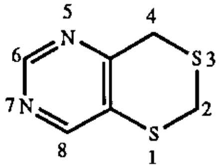


122



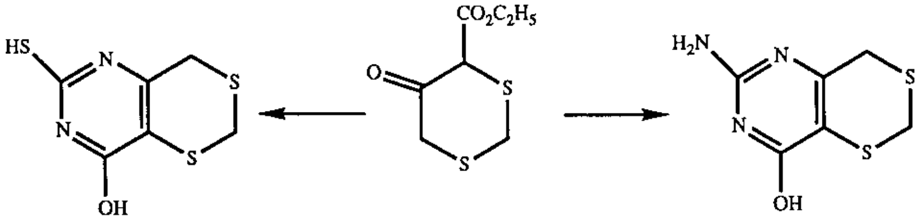
123

8. 4*H*-1,3-DITHIINO[5,4-*d*]PYRIMIDINES



21

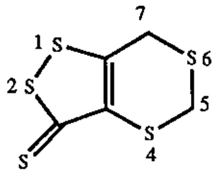
6-Mercapto-4*H*-1,3-dithiino[5,4-*d*]pyrimidin-8-ol (**125**) was prepared (26%) from ethyl 5-oxo-1,3-dithiane-4-carboxylate (**124**) and thiourea.[59] The 6-amino derivative (**126**) was prepared similarly from compound **124** and with guanidinium thiocyanate. Condensation of the methyl ester of **124** gave the 6,8-dihydroxy compound.[57]



(28)

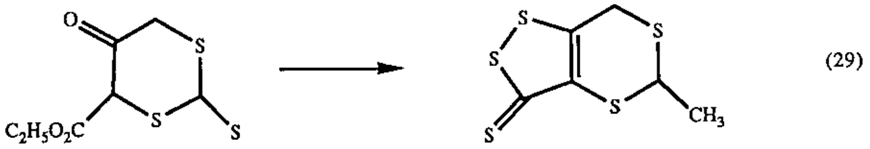
125 **124** **126**

9. 1,2-DITHIOLO[4,3-*d*]-1,3-DITHIIN



22

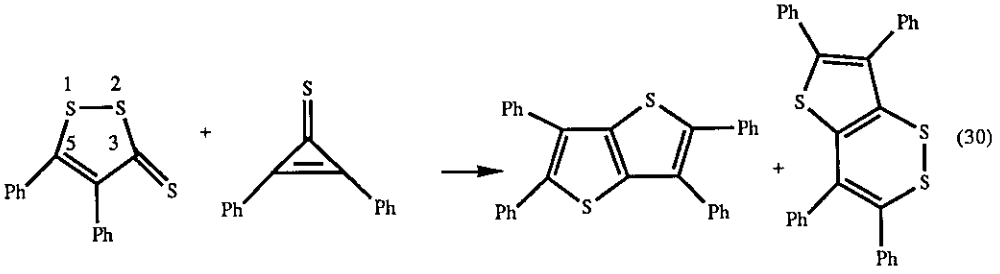
Treatment of 2-methyl-1,3-dithia-4-carbethoxycyclohexan-5-one (**127**) with P_4S_{10}, S, and CS_2 gave 5-methyl-1,2-dithiolo[4,3-*d*]-1,3-dithiin-(7<u>H</u>)-thione (**128**) which appears to be the only reported member of this family.[60]



127 **128**

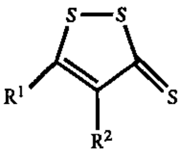
10. OTHER DERIVATIVES OF 4<u>H</u>-1,3-DITHIINS

4,5-Diphenyl-1,2-dithiole-3-thione (1,2-trithione, **129**) reacts with 2,3-diphenylcyclopropenethione (**130**) to give thieno[3,2-*b*]thiophene (**131**) and tetraphenylthieno[3,2-*c*]-1,2-dithiin (**132**).[118]

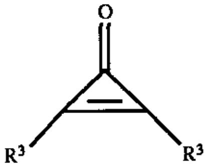


129 **130** **131** **132**

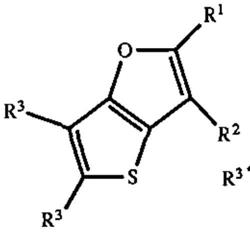
1,2-Trithiones (**129**, **133**) react with 2,3-diarylcyclopropenones (**130**, **134**) to give the corresponding thieno[3,2-*b*]furans (**135**), 1,2-dithiole-3-ones (**136**), and 4*H*-1,3-dithiin **137a** and/or **137b**. A mechanism for formation of **137a** and **137b** is shown in Scheme V.[118]



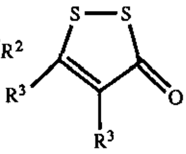
129 $R^1 = R^2 = C_6H_5$
133a $R^1 = C_6H_5$; $R^2 = CH_3$
133b $R^1 = R^2 = CH_3$
133c $R^1 - R^2 = -(CH_2)_4-$
133d $R^1 - R^2 = -(CH{=}CH)_2-$
133e $R^1 = CH_3$; $R^2 = C_6H_5$



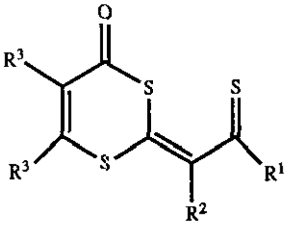
130 $R^3 = C_6H_5$
134a $R^3 = 4\text{-}ClC_6H_4$
134b $R^3 = 4\text{-}CH_3C_6H_4$
134c $R^3 = CH_3, C_6H_5$



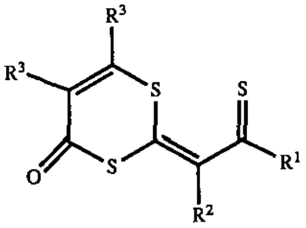
135



136

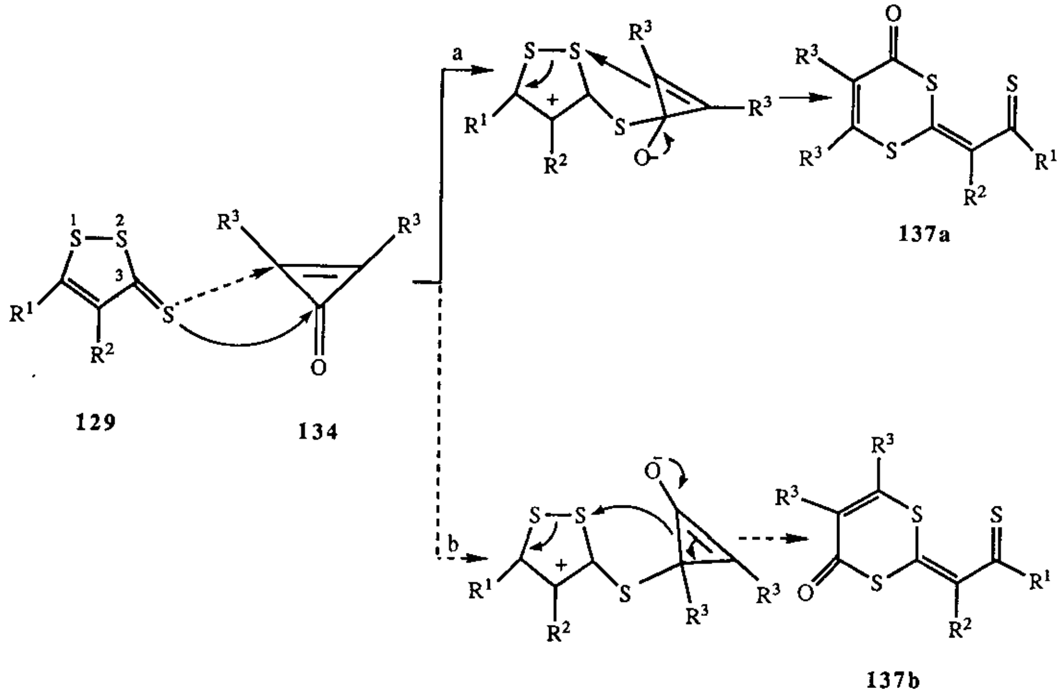


137a

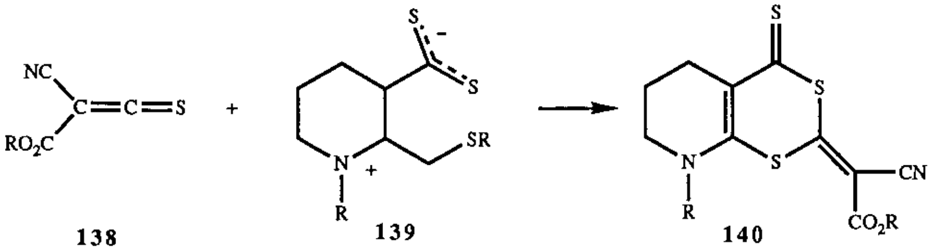


137b

Scheme V

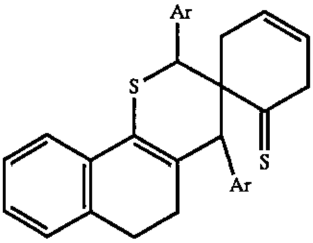


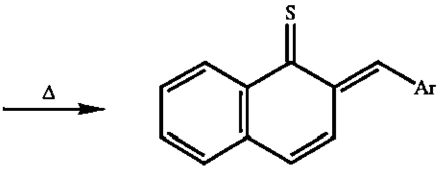
The 1,4-dipole (**139**) reacts with thioketene (**138**) to give the cycloadduct (**140**).[119,120]



(31)

2-(Arylmethylene)tetralin-1-thiones (**142**) and thiochalcones (**144**), which were generated by thermolysis of their respective dimers (**141** and **143**), undergo cycloaddition reactions with various dienophiles to give a wide variety of products.[64,121]

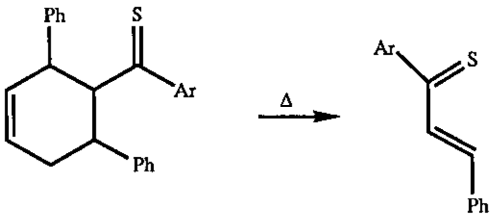




(32)

141a Ar = C_6H_5
141b Ar = 4-$CH_3OC_6H_4$
141c Ar = 4-ClC_6H_4

142

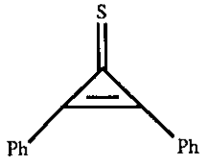


(33)

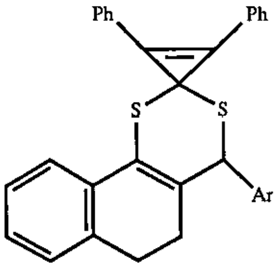
143a Ar = C_6H_5
143b Ar = 4-$CH_3OC_6H_4$
143c Ar = 4-ClC_6H_4

144

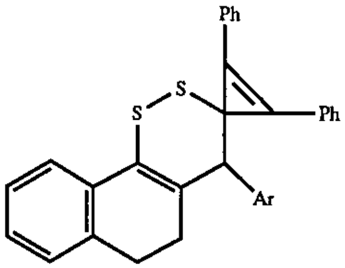
Treatment of the thione (**142**) with 2,3-diphenyl-2-propene-1-thione (**130**) in refluxing benzene (1 h) gave 1:1 adducts (56-63%) for which the regioisomeric structures (**145**) (5',6'-dihydro-2,3,4'-triarylspiro[2-cy-clopropene-1,2'-[4H]-naphthol[1,2-*d*][1,3]dithiin]) and **146** are reason-able.[123] Structure **145** was preferred owing to the extrusion of a phenylmethanethial molecule in the mass fragmentation pattern. Similarly the reaction of **130** and **143** gave the 6'-aryl-2,3,4'-triphenylspiro[2-cyclopropene-1,2'-[4H][1,3]dithiins (**147**, 62-88%).[121]



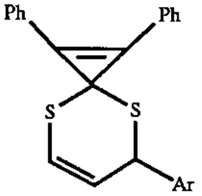
130



145



146

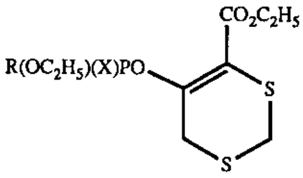


147

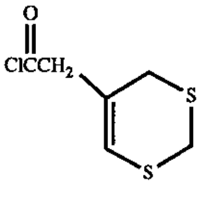
11. BIOACTIVITY

3-Ethenyl-3,4-dihydro-1,2-dithiin (**11**) and 2-ethenyl-4H-1,3-dithiin (**12**) show antithrombotic activity.[53]

Although the garlic constituents (E/Z) ajoene and dially disulfide strongly inhibited prostaglandin synthease and 5-lipoxygenase, which are involved in prostaglandin and leukotriene biosynthesis, respectively, 3-ethenyl-3,4-dihydro-1,2-dithiin (**11**) and 2-ethenyl-4H-1,3-dithiin (**12**) did not inhibit the enzymes to any appreciable extent.[122] 1,3-Dithiacyclohexenyl (thiono)(thiolo)phosphoric(phosphonic) acid esters (**148**, X = S, R = OC_2H_5, SC_3H_7, C_2H_5, Ph; X = O, R = OC_2H_5) have found applications as insecticides.[123] Compound **148** (X = S, R = OC_2H_5) at 5 ppm gave 100% kill of *Porbia antiqua* larvae in soil.



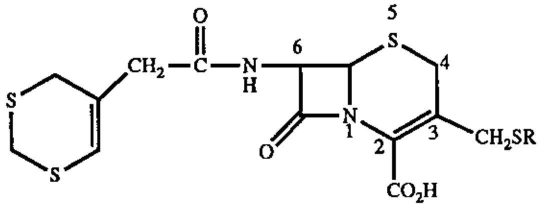
148



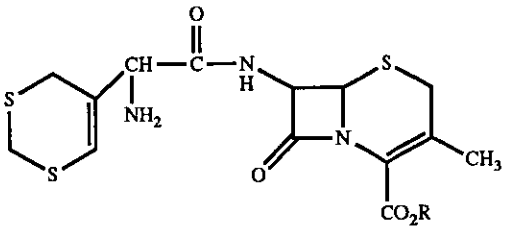
149

The cephalosporin derivatives (**150**, R = 5-methyl-1,3,4-thiadiazol-2-yl, 1-methyl-5-tetrazolyl) were prepared by the reaction of 7-aminocephalosporanic acid with **149**, followed by reaction with 5-methyl-2-thioxo-

1,3,4-thiadiazoline or 1-methyl-5-thioxotetrazoline. Compounds **150** are useful as bactericides, *e.g.* at 0.1-0.5 μg/cm^3 in vitro against *Staphylococcus aureus* Smith.[124]



150



151

Other cephalosporin derivatives (**151**, R = H, $CHR^1O_2CR^2$; R^1 = H, C_{1-4} alkyl; R^2 = C_{1-4} alkyl, cyclohexyl) and their salts were prepared for use as bacteriocides.[125,126]

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