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Naturally Occurring 1,2-Dithiolanes and 1,2,3-Trithianes. Chemical and Biological Properties

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NATURALLY OCCURRING 1,2-DITHIOLANES AND 1,2,3-TRITHIANES. CHEMICAL AND BIOLOGICAL PROPERTIES.

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This review describes the synthesis as well as the physical and chemical properties of naturally occurring 1,2-dithiolanes and 1,2,3-trithianes. Data on synthetically prepared model compounds are included as background material. The natural occurrence and function, and additional biological activities of these compounds are summarized. Practical applications of chemical and biological properties are presented.

Reagents for the syntheses and chemical transformations as well as physical properties (spectroscopic data, electrochemical data, melting points) are recorded in appropriate tables.

The literature is covered extensively from the first half of 1970 up to the end of 1987. References prior to the former date are included when considered relevant to the current discussion. References from Chemical Abstracts, Vols. 108 and 109 are collected in the addendum. Reports which are not immediately available in English, French or German are cited from Chemical Abstracts.

Key words: 1,2-Dithiolanes, 1,2,3-trithianes, synthesis, natural occurrence, biological activities, practical applications.

CONTENTS

INTRODUCTION

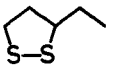
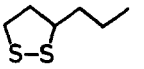
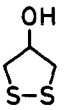
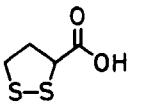
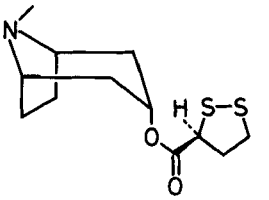
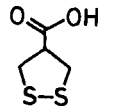
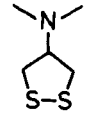
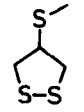
The 1,2-dithiolanes and 1,2,3-trithianes constitute a group of compounds with a widespread occurrence in nature. Representatives with varying substitution patterns have been isolated from animal tissue — ranging from eucariots through higher vertebrates to mammals —, and from plants — algae as well as higher plants.

These compounds — especially the 1,2-dithiolanes — differ drastically from their open-chain counterparts, as well in their chemical and physico-chemical properties as in their functions in biological systems.

The 1,2-dithiolane ring system was first described at the end of the last century.[1,2] In the late thirties an extensive study of the synthesis and structure elucidation of substituted 1,2-dithiolanes and 1,2,3-trithianes followed,[3-5] and at the same time the first naturally occurring 1,2-dithiolane [nereistoxin, 4-(*N,N*-dimethylamino)-1,2-dithiolane] was isolated.[6] The structure of this compound, however, was established only thirty years later.[7,8]

Around 1950 the interest in the 1,2-dithiolane ring system grew enormously with the discovery that lipoic acid, *i.e.* 5-(1,2-dithiolan-3-yl)pentanoic acid, is responsible for the transfer of acetyl groups from pyruvic acid to coenzyme A and thereby for the feeding of carbon into the Krebs cycle.[9-13] At the same time it was recognized that the, necessarily small, dihedral angle around the S–S bond in these small rings is, at least partly, responsible for the enhanced reactivity and consequently lowered stability of 1,2-dithiolanes.[14,15] These findings prompted an intense research on this subject, and not one year has passed without new chemical, biological or biochemical contributions. At this date a total of more than twenty 1,2-dithiolanes and 1,2,3-trithianes have been identified from natural sources. These naturally occurring compounds are listed in Table 1.

Table 1. Naturally occurring 1,2-dithiolanes and 1,2,3-trithianes (melting points are given when reported).

Compound	trivial name	formula	m.p. (°C)[ref.]
1,2-dithiolane			
3,3-Dimethyl-	-		-
3-Ethyl-	-		-
3-Propyl-	-		-
3,4-Dimethyl-	-	 both isomers	-
4-Hydroxy-	-		-
-3-carboxylic acid	-		81–82[24]
--tropinyl ester	brugine		-
-4-carboxylic acid	asparagusic acid		75.7–76.5[25] (polym.[36])
4-(*N*,*N*-Dimethylamino)-	nereistoxin		-
4-(Methylthio)-	charatoxin		-

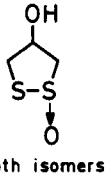
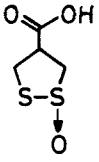
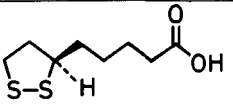
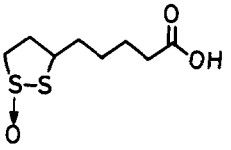
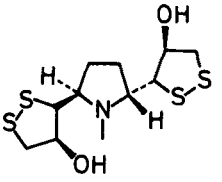
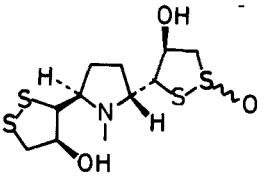
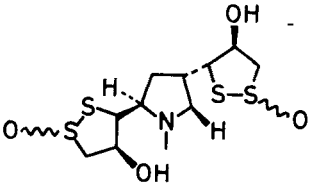
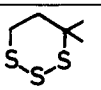
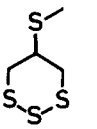
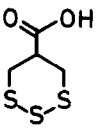
1,2-dithiolane 1-oxide			
4-Hydroxy-	brugierol	 both isomers	(*anti*) 84[258]
-4-carboxylic acid	-	 both isomers	(*syn*) 118.5–120[287] (*anti*) 127–128.5[287]
pentanoic acid			
5-(1,2-Dithiolan-3-yl)-	lipoic acid		47.5–48.5[9]
5-(1-Oxo-1,2-dithiolan-3-yl)-	β-lipoic acid		-
pyrrolidine			
1-Methyl-2,5-bis(4-hydroxy-1,2-dithiolan-3-yl)-	gerrardine		180–181[256]
1-Methyl-2-(1-oxo-4-hydroxy-1,2-dithiolan-3-yl)-5-(4-hydroxy-1,2-dithiolan-3-yl)-	"gerrardine monooxide"		-
1-Methyl-2,5-bis(1-oxo-4-hydroxy-1,2-dithiolan-3-yl)-	"gerrardine dioxide"		-

Table 1. Continued

Compound	trivial name	formula	m.p. (°C)[ref.]
1,2,3-trithiane			
4,4-Dimethyl-	-		-
5-(Methylthio)-	-		-
-5-carboxylic acid	-		-

1. SYNTHESIS

Although a large number of syntheses of 1,2-dithiolanes and 1,2,3-trithianes have been reported, only a few general routes of formation of these compound exists. Referring to the sulfur reagent used four distinct types of reaction may be discerned.

Type 1. Reactions with nucleophilic sulfur species which lead to immediate ring formation (Table 2, entries 1–25).

Type 2. Reactions with nucleophilic sulfur species which give ring formation by hydrolysis of the primarily formed product (Table 2, entries 26–29).

Type 3. Reactions using nucleophilic sulfur species yielding a primary product which is hydrolyzed or reduced to a 1,3-dithiol and subsequently oxidized to the desired ring compound (Table 2, entries 30–85).

Type 4. Reactions using electrophilic sulfur species (Table 3).

In virtually all of the described syntheses the sulfur atoms are introdued by substitution reactions. The only exception encountered is the synthesis of lipoic acid in which the first sulfur atom is introduced via a Michael addition.[10,16–20] Thus, the array of sulfur reagents available for the formation of 1,2-dithiolanes and 1,2,3-trithianes is the same as that described for the synthesis of open-chain di- and trisulfides.[21a] However, as shown in the following sections, the merits of the individual methods may differ significantly when the ring syntheses are compared to the syntheses of the open-chain compounds.

1.1. Substitution

1.1.1. Nucleophilic substitution The nucleophilic sulfur reagents encountered in the literature are summarized in Table 2. The difunctional electrophilic substrates on which

Table 2. Nucleophilic sulfur reagents employed in the synthesis of 1,2-dithiolanes and 1,2,3-trithianes.

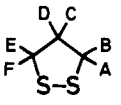
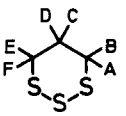
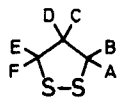
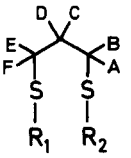
Entry	substrate type (leaving group)	product*	yield (%)	ref.
Type 1 nucleophile: S_2^{2-}				
1	A(Br)		9[a]	15
2	A(Br)	C,D = -$(CH_2)_5$-	21[b]	3
3	A(Br)	C = D = -CH_2OH	57	3
4	A(Br)	C = D = Me	55	4
5	A(Br)	A = F = -COOH	11/22	23/18
6	A(Br)	C,D = -(CH_2SSCH_2)-	-	26
7	A(Cl)	A = -$(CH_2)_4CO_2Et$	68	18
8	A(Cl)	A = -$(CH_2)_4COOH$	46	18
				
9	A(Br)	C,D = -(CH_2SCH_2)-	23	4
10	A(Cl)	D = -NMe_2	71	91
Type 1 nucleophile: S_4^{2-}				
11	A(Br)	C,D = -$(CH_2)_5$-	-	3
12	A(Br)	C = D = Me	-	3
13	A(Br)	C,D = -(CH_2SSSCH_2)-	54	5
14	C(OBs)	C,D = -$(CH_2)_5$-	-	38
15	A(Cl)	D = -OH	70	57
16	C(OMs)	C = D = Me	79	45
17	C(OMs)	C = D = Et	70	45
18	C(OMs)	C = D = *i*-Bu	55	45
19	C(OMs)	C = Me, D = *neo*-pentyl	62	45
20	C(OMs)	C = Me, D = Ph	49	45
21	C(OMs)	C = Me, D = *i*-Bu	74	45
				
22	A(Br)	C,D = -$(CH_2)_5$-	52[c]	3
23	A(Br)	C = D = -CH_2OH	94	3
24	A(Br)	C,D = -(CH_2SSCH_2)-	36[c]	5
25	C(OBs)	C,D = -$(CH_2)_5$-	47[c]	38

Table 2. Continued

Entry	substrate type (leaving group)	product*	yield (%)	ref.
Type 2 nucleophile: ^-SCN		 $R_1 = R_2 = -SCN$		
26	A(Br)		83	1
27	A(Cl)	A = $-(CH_2)_4COOH$	-	18
Type 2 nucleophile: $S_2O_3^{2-}$		$R_1 = R_2 = -SO_3Na$		
28	A(Br)		60[d]	14
29	A(Cl,Br)	C,D = = O	-	30
Type 3 nucleophile: HS^-				
30	A(Cl)	C,D = = O	59[e]	30
31	A(Cl)	A = $-(CH_2)_4CO_2Et$, C, D = = O	65[f]	30
32	A(Br)		34	31
33	A(Br)	A = Me	30	31
34	A(Br)	A = E = Me	14	31
35	A(Cl)	A,B = = O	50	518
36	A(Cl)	A,B = = O, C = Me	30	518
37	A(Cl)	A,B = = O, E = Me	30	518
38	A(Br)	A,B = = O, E = We	29	518
Type 3 nucleophile: CH_3S^-		$R_1 = R_2 = Me$		
39	A(Cl)	C = $-NMe_2$	43[g]	34
Type 3 nucleophile: $PhCh_2S^-$		$R_1 = R_2 = -CH_2Ph$		
40	A(Br)	C = $-CO_2Et$	93	27
41	A(Br)	A = $-CONH_2$	68	28
42	A(Cl)	C = -OH	55	33
43	A(Br)	C = $-NMe_2$	61[g]	34
44	A(Cl)	C = 1-pyrrolidinyl	-	34
45	A(Cl)	C = 1-piperidinyl	-	34
46	A(Cl)	C = 4-morpholinyl	-	34
47	A(Cl)	C = 2-methylpiperidin-1-yl	-	34
48	A(Cl)	C = $-NPr_2$	-	34
49	A(Cl)	A = $-(CH_2)_4CO_2Et$	75–82	35
50	A(Br)	A = -COOH	66[d,f,h]	18
51	C(OTs)	A = $-(CH_2)_4COOH$	33[f,h]	16
52	A(Br)	C,D = =O	100	42
53	D	A = $-CH_2CO_2Me$	-	18

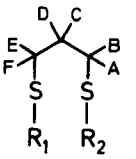
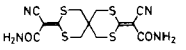
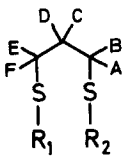
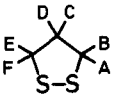
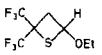
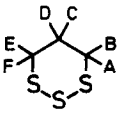
		other products		
54	D	$PhCH_2S(CH_2)_2CO(CH_2)_4CO_2Et$	66–97	16
55	D	$PhCH_2S(CH_2)_2CHO$	-	18
Type 3 nucleophile: CH_3COS^-				
56	D	$CH_3COS(CH_2)_2CO(CH_2)_4CO_2Et$	–/91	10/17
57	D	$HO_2CCH_2CH(SAc)(CH_2)_4CO_2Et$	-	19
		 $R_1 = R_2 = Ac$		
58	A(I)	C = –COOH	17[d,f]	22
59	A(Br)	A = $-CO_2Me$	80	24
60	A(Br)	A = $-CO_2Et$, E = *n*-Bu	60	29
61	A(Cl,Br)	A = $-CO(CH_2)_3CO_2Me$	81	30
62	A(Cl)	A = $-(CH_2)_4CO_2Et$, C, D = =O	79	30
63	A(Cl,Br)	A = Ac	78	30
64	A(Cl)	C,D = =O	-	30
65	A(Br)	A = $-(CH_2)_4CO_2Et$	60–68[d,f]	35
Type 3 nucleophile: CS_3^{2-}		$R_1,R_2 = >C=S$		
66	A(I)	C = –COOH	28	25
Type 3 nucleophile: 		$R_1,R_2 = >C=C$ CN / $CONH_2$		
67	C(OTs)	C = D = $-CO_2Et$	60	36
68	C(OTs)	C = Et	80	36
69	C(OTs)	C = D = Et	42	36
70	A(Br)		63	36
Type 3 nucleophile: $(H_2N)_2CS/HI$		$R_1 = -C(NH_2)_2^+$, R_2 = H		
71	B	A = $-(CH_2)_4COOH$	49[d]	17
72	B	A = $-(CH_2)_4COOH$	32[d,f]	10
		R_1 = H, $R_2 = -C(NH_2)_2^+$		
73	B	A = $-(CH_2)_4COOH$	-	19

Table 2. Continued

Entry	substrate type (leaving group)	product*	yield (%)	ref.
Type 3 nucleophile: $(H_2N)_2CS/HI$		 $R_1 = R_2 = -C(NH)_2^+$		
74	B,C(OMe)	A = $-(CH_2)_4COOH$	26[d,f]	37
75	C(OMe,OAc)	A = $-(CH_2)_4COOH$	42[d,f]	37
76	C(OMe,-OCOR)	A = $-(CH_2)_4COOH$	49[d,f]	37
77	C(OAc)	A = $-(CH_2)_4COOH$	40[d,f]	37
78	C(OEt)	A = $-(CH_2)_4COOH$	62[d,f]	37
79	B	A = $-(CH_2)_4COOH$	25[d,f]	37
80	B,C(OEt)	A = $-(CH_2)_4COOH$, C = Me	19[d]	30
81	B,C(OEt)	A = $-CH_2CH(CH_3)(CH_2)_2COOH$	59[d]	30
82	B	A = $-(CH_2)_4COOH$	-	19
83	C(OAc,-OCOR)	A = $-(CH_2)_4COOH$	19[d,f]	19
Type 3 nucleophile: $(H_2N)_2CS$				
84	A(Br)	A = B = Me	37[d]	32
85	A(Br)	A = B = E = F = Me	-	32
Miscellaneous sulfur reagents: $H_2/H_2S/CoS$				
86	keton	A = $-(CH_2)_4COOH$, R_1 = H, R_2 = $PhCH_2-$	12[f,h]	16
87	D	A = $-(CH_2)_4COOH$, R_1, R_2 = Co^{2+}	30–39[d,f]	18
$S_8/NEt_3/DMF$				
88		A = −OEt, E = F = $-CF_3$	57	60
$S^{2-}/S_8/DMF$				
89	A(Br)	A = Pr	-	69
90	A(Br)	A = Et	-	67/70
91	A(Br)	A = B = Me	-	68
92	A(Br)	A = C = Me	-	68
93	C(OMs)	A = $-(CH_2)_4CO_2Me$	-	84
94	C(OMs)	A = $-(CH_2)_4CO_2i$-Pr	65	86
95	C(OMs)	A = $-(CH_2)_4CO_2Et$	70	89

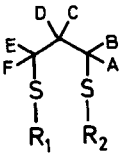
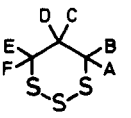
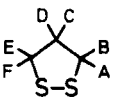
S_8/DMF				
96		C = D = $-CO_2Et$	20[a]	54
S_8/$PrNH_2$				
97		C = $-NMe_2$[i]	-	59
S^{2-}				
98		$R_1 = R_2 = SO_3Na$	26	40
99		C = $-NMe_2$[i]	79	41

* Substituents different from H are given.
a. Yield determined by spectroscopic methods.
b. Isolated as the $HgCl_2$ adduct.
c. Yield calculated after desulfurization.
d. Yield calculated after hydrolysis.
e. Yield calculated after $NaBH_4$ reduction and treatment with Ac_2O.
f. Yield calculated after oxidation.
g. Yield calculated from indirect data.
h. Yield calculated after reduction with Na/NH_3.
i. Isolated as the hydrogen oxalate.

they are used are as a rule: halides,[1,3-5,14,18,22-36] (type A), alcohols[17,19,30,37] (type B) or derivatives of alcohols[16,19,30,36-38] (Type C). The α,β-unsaturated carbonyl compounds (type D) which are used as starting materials in many syntheses of lipoic acid (Sect. 1), are included in Table 2.

A few remarks can be made on the basis of Table 2. The two related type 1 reagents, S_2^{2-} and S_4^{2-}, both give cyclic products. The former yields 1,2-dithiolanes and the latter

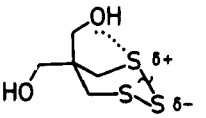
Table 3. Electrophilic sulfur reagents employed in the synthesis of 1,2-dithiolanes and 1,2,3-trithianes.

Entry	substrate*	product*	yield (%)	ref.
				
Sulfur reagent: SCl_2				
1	C = D = Et	C = D = Et[a]	75	45
2	C,D = $-(CH_2)_5-$	C,D = $-(CH_2)_5-$[a]	65	45
3	C,D = $-(CH_2)_4-$	C,D = $-(CH_2)_4-$[a]	68	45
4	C = Me, D = Et	C = Me, D = Et[a]	72	45
5	C = Me, D = Pr	C = Me, D = Pr[a]	69	45
6	C = Me, D = *i*-Pr	C = Me, D = *i*-Pr[a]	58	45
7	C = Me, D = Bu-2-yl	C = Me, D = Bu-2-yl[a]	57	45
8	[b]		43	46
9	$R_1 = R_2 = SiMe_3$[c]		31	46
10	$R_1 = R_2 = SiMe_3$[d]		75	46
11	$R_1,R_2 = >SiMe_2$		49	46
12	$R_1 = R_2 = SnPh_3$		36	46
13	$R_1,R_2 = >SnMe_2$		30	46
Sulfur reagent: $S_2O_3Na_2/H_3O^+$				
14	C,D = $-(CH_2OCH_2)-$ $R_1 = R_2 = -SO_3Na$	C,D = $-(CH_2OCH_2)-$	-	183
Sulfur reagent: S_2Cl_2				
15	PhNHCOCH$_2$COCH$_2$COCHPh	A = E = -CONHPh, C,D = =O	-	18

* Substituents different from H are given.
a. In mixture with the corresponding 1,2-dithiolane.
b. Catalyst: NEt_3.
c. Substrate conc.: 1.2×10^{-1} M.
d. Substrate conc.: 1.9×10^{-2} M.

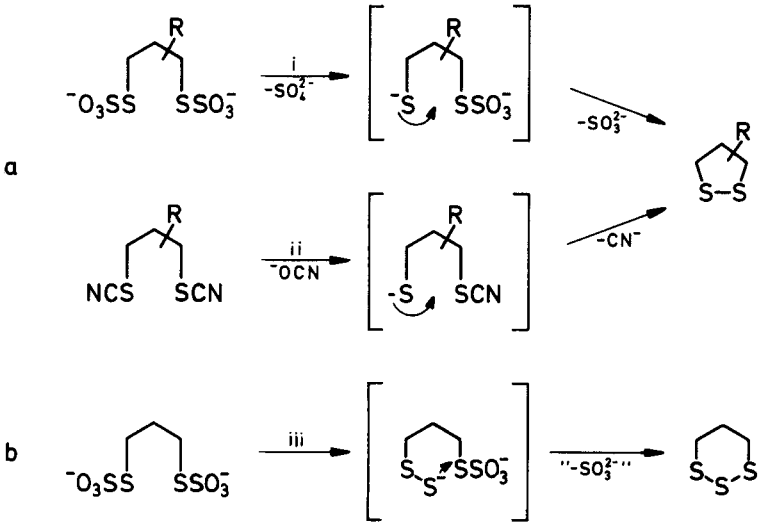
normally yields a mixture of 1,2-dithiolanes and 1,2,3-trithianes which are easily desulfurized (Sect. 1.3) if the 1,2-dithiolanes are the desired products. However, when these two reagents are applied to the same substrate S_4^{2-} tends to give the higher yield (Table 2, entries, 2, 3, 22, 23 and 25). As an exception the reaction between S_4^{2-} and 2,2-bis-(bromomethyl)-1,3-propanediol does not produce a trithiane;[3,18,39] 4,4-bis(hydroxymethyl)- 1,2-dithiolane is formed directly in almost quantitative yield (Table 2, entry 23). A possible explanation of this fact is an anchimerically assisted heterolytic cleavage of

one S–S bond in which a partial positive charge is stabilized by an oxygen lone pair (Formula **1**).



(1)

The two type 2 reagents give ring formation upon hydrolysis. Since no dithiol intermediates are found a cyclic mechanism is believed to operate[32] (Schemes 1a,b). The basic hydrolysis of 6,8-bis-(thiocyanato)octanoic acid has successfully been applied to the synthesis of lipoic acid.[18] In an alternative reaction (Scheme 1b) a sulfur atom of a bis(thiosulfate) is attacked by the softer nucleophile, S^{2-}. This reaction has been used for the preparation of a 1,2,3-trithiane[40] (Table 2, entry 98). A related reaction is the patented[41] preparation of 5-(*N*,*N*-dimethylamino)-1,2,3-trithiane — a powerful insecticide — by treatment of the hydrochloride of 4-(*N*,*N*-dimethylamino)-1,2-dithiolane 1-oxide with sulfide ion (Table 2, entry 99).



Scheme 1. i: H_2O, ii: OH^-, iii: S^{2-}

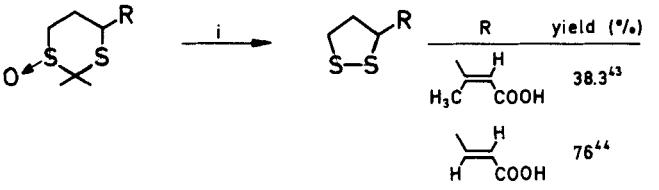
The type 3 reagents constitute the largest group of sulfur nucleophiles encountered in the literature (Table 2, entries 30–85). These reagents all react readily with electrophilic substrates bearing good leaving groups, *e.g.* types A and C (only sulfonates), whereas catalytic activation is necessary for substrates with poorer leaving groups, *e.g.* types B and C.

The material collected in Table 2 is meant to provide a guide for the selection of the proper sulfur reagent for a given reaction. The actual choice of reagent is dependent on the functionalities in the target molecule since the transformation of the initial substitution product into a 1,3-dithiol can be accomplished in several ways. As an illustrative example the two most commonly used reagents, phenylmethanethiolate ion

($PhCH_2S^-$)[16,18,27,28,33-35,42] and thioacetate ion (CH_3COS^-)[10,17,19,22,24,29,30,35] give comparable yields of intermediates (Table 2, entries 40–52 and 58–65). In the subsequent stage the 1,3-dithiols are generated by reduction of the former, but by hydrolysis of the latter intermediates.

Mild basic conditions prevail in the aminolysis of the intermediate 1,3-dithiane formed by the application of disodium 2-carbamoyl-2-cyanoethylene-1,1-dithiolate[36] (Table 2, entry 67–70). Similar reaction conditions might conceivably be applied to the cleavage of the 1,3-dithian-2-thiones formed by the application of trithiocarbonate ion[25] (Table 2, entry 66) although no examples are known. The standard procedure in this case has been acid hydrolysis. These two sulfur nucleophiles are particularly interesting when dealing with sterically hindered, or otherwise sluggishly reacting, electrophiles since being dianions they are more powerful nucleophiles in the first substitution step, and the second substitution, giving the 6-membered ring, is entropy favored. The yields of substitution products with monothiolates vary strongly with the reactivity of the electrophile (Table 2, entries 67–69, 59, 60 and 32–34).

An alternative route to 1,2-dithiolanes involving 1,3-dithianes as intermediates has recently been patented.[43,44] 1,3-Dithianes are oxidized to 1-oxides which by ring contraction yield 1,2-dithiolanes on treatment with acid (Scheme 2).



Scheme 2. i: H_2O/dioxane/H_2SO_4/heat

1.1.2. Electrophilic substitution 1,2-Dithiolanes are normally synthesized by nucleophilic substitution reactions (Sect. 1.1.1); only a single example of electrophilic substitution is described[18] (Table 3, entry 15). 1,2,3-Trithianes, however, are generally accessible by electrophilic substitution of substrates already containing two sulfur atoms, *i.e.* 1,3-dithiols or derivatives. Table 3 summarizes the electrophilic sulfur reagents employed and the nucleophilic substrates with which they have been used.

One work[45] compares the synthesis of 1,2,3-trithianes by nucleophilic and electrophilic substitution and establishes that there is no significant difference in the yields obtained by the two routes. By either procedure the 1,2-dithiolane is formed concomitant with the desired 1,2,3-trithiane. However, the yield of 1,2,3-trithiane can be improved by conversion of the substrate thiol groups into stannyl or silyl sulfides prior to the treatment with sulfur dichloride[46] (Table 3, entries 8–13). In particular, 1,3-bis(trimethylsilyl) sulfides seem to be suitable substrates for this sulfur electrophile (Table 3, entry 10). This method has been patented.[47]

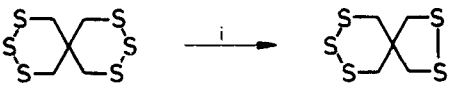
1.2. Oxidation

Since 1,2-dithiolanes are prone to polymerization (cf.[15]) — thermally as well as photolytically — it can be advantageous to follow a preparative route which involves a type

3 nucleophile, because the oxidation of the 1,3-dithiols, formed by cleavage of the intermediate substitution products, may be carried out under mild conditions. A number of oxidizing agents are listed in Table 4. Almost all mild oxidants are capable of transforming 1,3-dithiols into 1,2-dithiolanes. Some 1,3-dithiols are oxidized even by air,[33,34,36] however the yields are raised by adding oxygen.[36] Iodine is the oxidant most commonly used either unaided [3,15,18,24,29,48] (Table 4, entries 3–10) or in the presence of various catalysts[10,15,16,19,27,28,30,32,49–52] (Table 4, entries 11–32). Addition of triethylamine to maintain neutral conditions during the oxidation seems to improve the yields by suppressing polymerization.[50] Iodine or bromine oxidation of alkyltinthiolates is reported to be a useful preparative route to cyclic disulfides of varying ring size.[53]

1.3. Sulfurization-Desulfurization Reactions

1,2-Dithiolanes and 1,2,3-trithianes are interconvertible by a number of sulfur insertion-extrusion reactions. The sulfur nucleophile S_4^{2-} (Sect 1.1.1) produces 1,2-dithiolanes as a mixture with 1,2,3-trithianes and, in a single case, a 1,2,3,4-tetrathiepane.[54] These reaction mixtures have been desulfurized with copper[3,5,38] under the conditions given in Table 5. When the desulfurization of 2,3,4,8,9,10-hexathioaspiro[5.5]undecane (Table 5, entry 4) is performed with potassium sulfide[5] only a single sulfur atom is removed (Scheme 3).



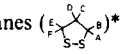
Scheme 3. i: K_2S in EtOH. Reflux 30 min.

Desulfurization of organic sulfur compounds has successfully been accomplished by the use of trivalent phosphorus compounds, especially tris(dialkylamino)phosphines.[55 and refs herein] These reactions take place under mild conditions in excellent yield. Examples are given in Table 6.

As a result of the large differences in reaction rates between disulfides and trisulfides — *e.g.* rate(dibenzyl trisulfide)/rate(dibenzyl disulfide) = 1.7×10^4 at 30 °C by the use of tris(diethylamino)phosphine — no sulfides are formed in the desulfurization of trisulfides.[55] It is therefore possible that this method could be applied to the transformation: 1,2,3-trithiane → 1,2-dithiolane in spite of the fact that 1,2-dithiolanes produce thietanes with the same reagent[50,56] (Table 6).

An example of oxidative desulfurization is found in a reaction sequence leading to the brugierols.[57] A mechanism has been proposed[58] for the desulfurization step (Scheme 4). In the present case the 4-hydroxy-1,2-dithiolane formed as intermediate is oxidized *in situ*. It seems probable, however, that use of stoichiometric amounts of *m*-CPBA would allow isolation of the 1,2-dithiolane prior to further oxidation.

Elemental sulfur has been reported[54,59,60] to act as sulfurization agent by an unknown mechanism producing 1,2,3-trithianes[54,59] and 1,2,3,4-tetrahiepane[54] from 1,2-dithiolanes and 1,2-dithiolanes from thietanes.[60] Use of a sulfur transferring agent — *N,N'*-thiobis(benzimidazole) — on dithiols produces only polymeric products instead of small and medium sized rings. The same result is obtained by the basic decomposition of bis(sulfenyl)thiocarbonates — an alternative synthesis of cyclic trisulfides.[61,62]

Table 4. Oxidants employed in the oxidation of 1,3-dithiols ( R = H)* to give the corresponding 1,2-dithiolanes ()*

Entry	substrate	yield (%)	ref.
Oxidant: Br_2			
1		–[a]	2
2	A = E = Me	5	31
Oxidant: I_2			
3	A = E = Me	5	31
4		102[b]	15
5	C,D = $-(CH_2)_5-$	40[c]	3
6	A = –COOH	15[d]	24
7	A = –COOH, E = Bu	27	29
8	C = –SMe	90–100[e]	48
9	C,D = =O	–	18
10	C = $-SO_3H$	–	18
Oxidant: I_2/NEt_3			
11	C = –COOH	40	49
12		56[b]	50
13	C = Ph	73	50
14	C,D = =O	–	50
Oxidant: $I_2/FeCl_3$			
15		26[b]	51
16		28–39[b]	32
Oxidant: I_2/KI			
17		100[b]	15
18	C = $-CH_2NH_3Cl$	65	27
19	B = $-CH_2NH_3Cl$	89	28
20	A = $-CH_2CH(CH_3)(CH_2)_4COOH$	54	30
21	A = $-(CH_2)_4COOH$, C = Me	10[d]	30
22	A = $-(CH_2)_4CO_2Et$, C,D = =O	–	30
23	A = $-CO(CH_2)_3COOH$	–	30
24	A = $-(CH_2)_4CO_2Me$, C = –OH	75	30
25	A = Ac	–	30
26	A = $-CHOHCH_3$	–	30
27	C = –OH	–	30
28	C,D = =O	–	30
29	A = $-(CH_2)_4COOH$	33[d]	16
30	A = $-(CH_2)_4COOH$	–	10,19,35
31	C = $-NMe_2$	> 38[f,g]	52
32	C = $-NH_2$	> 24[f,g]	52

Oxidant: KI/air			
33		–	15
Oxidant: KI/H_2O_2			
34	C = -COOH	57–85	49
35		70–84[b]	51
Oxidant: $H_2O_2/FeCl_3$			
36	A = -COOH	15[d]	24
Oxidant: *t*-BuOOH/$FeCl_3$			
37	A = B = Me	50	32
38	A = B = E = F = Me	–	32
Oxidant: $FeCl_3$			
39	A,B = =O, C = -NHCOPh, E = F = Me	50	18
40	A,B = =O, E = Me	74	518
Oxidant: $O_2/FeCl_3$			
41	A = $-(CH_2)_4COOH$	53	37
42	A = $-(CH_2)_4COOH$	82–85	35
43	A = $-(CH_2)_4COOH$	–	19/20
44	A = $-(CH_2)_4COOH$	61	17
45	C = -COOH	90	74
46	C = -COOH	–	22
47	A = -COOH	15[d]	24
48	A = -COOH	–	18
49	A = $-CH_2O(CH_2)_2COOH$	61	29
50	A = $-CH_2COOH$	10	18
51	A = E = -COOH	77	519
Oxidant: O_2			
52	C = D = $-CO_2Et$	91[h]	36
53	C = D = Et	95[h]	36
54	C = Et	34[h]	36
55	C = D = $-CH_2SH$	30[h]	36
Oxidant: air			
56	C = $-NMe_2$	$-/>42$[f,g]	33/34
57	C = 1-pyrrolidinyl	–	34
58	C = 1-piperidinyl	–	34
59	C = 4-morpholinyl	–	34
60	C = 2-methylpiperidin-1-yl	–	34
Oxidant: air/$FeCl_3$			
61	C = $-NMe_2$	>59[f,g]	52
62	C = -NHMe	>21[f,g]	52
63	C = $-NH_2$	>10[f,g]	52
64	C = $-NH_2$	35[g]	42

Table 4. Continued

Entry	substrate	yield (%)	ref.
65	C = -NHMe	61[g]	42
66	A = $-(CH_2)_4CONH_2$	-	520
Oxidant: air/OH^-			
67		-	15
Oxidant: *t*-Bu sulfenate/OH^-			
68		-	15
Oxidant: $(t\text{-BuS})_2/OH^-$			
69		-	15
Oxidant: $K_3Fe(CN)_6/OH^-$			
70	C = -COOH	32	49
Oxidant: DMSO			
71	C = COOH	70	25
Oxidant: DMSO/$SbCl_5$			
72		91	521
Oxidant: sulfur			
73	$R_1,R_2 = Pb^{2+}$	90	71
74	C = -OH, R_1,R_2 = Pb	79	71
Oxidant: $Pb(OAc)_4$			
75		21–40	51

* Substituents different from H are given.
a. The product polymerizes.
b. Determined by spectroscopic methods.
c. Isolated as the $HgCl_2$ adduct.
d. Calculated from indirect data.
e. Determined by GLC.
f. Substrate not isolated prior to oxidation.
g. Isolated as the hydrogen oxalate.
h. Oxidation takes place during aminolysis.

Table 5. 1,2-Dithiolanes by desulfurization of 1,2,3-trithianes ()* with copper in boiling toluene.

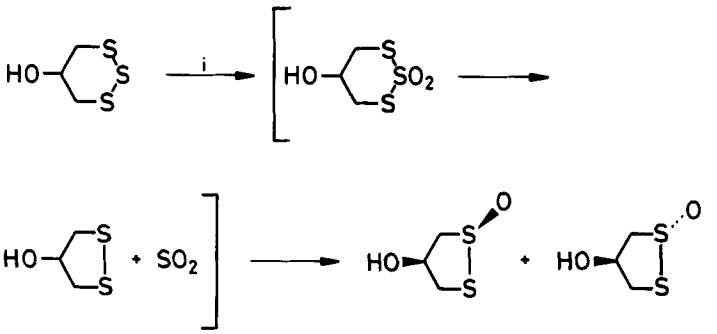
Entry	substrate	reaction time	yield (%)	ref.
1	C,D = $-(CH_2)_5-$	20 min.	80[a]	3
2	C,D = $-(CH_2)_5-$	30 min.	81–100[a]	38
3	C = D = Me	15 min.	–[b]	3
4	C,D = $-(CH_2SSSCH_2)-$	1 hour	67[a]	5

* Substituents different from H are given.
a. Calculated from indirect data.
b. The product polymerizes.

Table 6. Desulfurization of trisulfides and 1,2-dithiolanes with $(Et_2N)_3P$ to give disulfides and thietanes

Entry	substrate[a]	reaction conditions[b]	yield (%)	ref.
	R_1SSSR_2		disulfide	
1	$R_1 = R_2 = -CH_2Ph$	2–3 h	94	55
2	$R_1 = R_2 = 4\text{-}MeOC_6H_4-$	2–3 h	62	55
3	$R_1 = R_2 = -(CH_2)_2CH_3$	2–3 h	80	55
4	$R_1 = -CH_2Ph$, $R_2 = -(CH_2)_2CH_3$	2–3 h	100[c]	55
			thietane	
5	$A = -(CH_2)_4COOH$	4 h	0[d]	50, 56
6	$A = -(CH_2)_4CONHPh$	1 h	64	50, 56
7	$A = -(CH_2)_4CO_2THP$[e]	24 h (ethyl acetate)	82[f]	52, 56
8		432 h	82[g]	56
9	C,D = =O	0.1 h	0[h]	56
10	C = Ph	4 h (reflux)	87	56
11	A = Pr	2–3 h	–	69
12	A,B = =O, C = Me	–[i]	59	522
13	A,B = =O, E = Me	–[i]	53	522
14	A,B = =O, C = Me, D = Cl	–[i]	44	522

a. Substituents different from H are given.
b. Benzene solution at room temp., unless otherwise noted.
c. Determined by GC.
d. The reaction yielded only diethyllipoamide.
e. THP = tetrahydropyranyl.
f. Isolated as the free acid.
g. Isolated as the $HgCl_2$ adduct.
h. The reaction yielded only polymeric product.
i. Cf. ref.[522].



Scheme 4. i: excess *m*-CPBA

1.4. Separation Procedures

Since 1,2,3-trithianes virtually always are formed concomitantly with 1,2-dithiolanes and/or thietanes[63] and/or tetrathiepanes[54] the separation of the product mixture plays a major role in the isolation of pure compounds. Chromatographic methods are preferred in most cases. Preparative GC[45] (using glass columns to minimize desulfurization) as well as preparative TLC[46,54,63–65] have been applied successfully. Pentane, hexane and cyclohexane have been used as eluents for the purification of unpolar substituted 1,2,3-trithianes.[54,63] In the case of 1,2,3-trithianes bearing polar substituents, acetone, methanol, water and chloroform in varying proportions are used as eluents.[64,65] In both cases the separation is effected on silica gel plates.

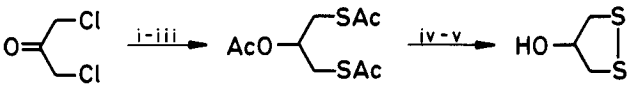
Column chromatography has been successfully applied to the separation of charatoxin from its trithiane counterpart[48,66] and this method is preferable to TLC and GC when dealing with compounds sensitive to air or elevated temperature, respectively.

1.5. Methods Applied to Naturally Occurring Compounds

The syntheses of the naturally occurring 1,2-dithiolanes and 1,2,3-trithianes follow the general trends described in the previous sections. Some of the more important reaction sequences, accompanied by a few comments and comparisons, are presented in the following paragraphs.

1.5.1. Alkyl substituted 1,2-dithiolanes and 1,2,3-trithianes Most of the synthetic work in this area has been carried out in support of structure elucidations of substances isolated from natural sources and little effort has gone into any optimization of the preparative routes. Syntheses (cf. Table 2, entries 89–92) of the following alkyl substituted 1,2-dithiolanes appear (yields given when recorded): 3-ethyl[67], 3,3-dimethyl (18.5%)[32,68], 3,4-dimethyl (*cis-trans* mixture and stereospecific *trans*)[68] and 3-propyl.[69,70]

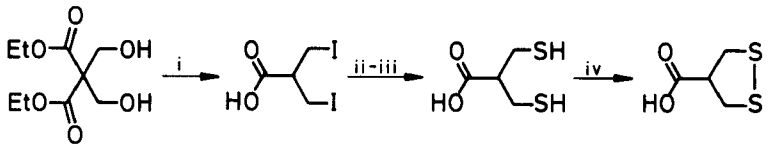
1.5.2. 4-Hydroxy-1,2-dithiolane 4-Hydroxy-1,2-dithiolane has been prepared from 1,3-dichloroacetone (Scheme 5).[30] The formation of 4-hydroxy-1,2-dithiolane by oxidation of the lead salt of 1,3-dimercapto-2-propanol with sulfur (79%)[71] and of the free dithiol with triethylammonio *N*-(methoxycarbonyl)sulfamate[72] has been reported.



Scheme 5. i: AcS^-/MeOH, ii: $NaBH_4$, iii: Ac_2O/AcO^-, iv: 2 M HCl, v: I_3^-

4-Hydroxy-1,2-dithiolane 1-oxide has been prepared (28%) by hydrogen peroxide oxidation of 4-hydroxy-1,2-dithiolane[72] (Table 7, entry 13) by oxidative ring contraction with *m*-CPBA (46%, Scheme 4) of 5-hydroxy-1,2,3-trithiane (Table 2 entry 15)[57] and by electrosynthesis from 2-(4-methoxyphenyl)-5-hydroxy-1,3-dithiane (62%)[73] (see Sect. 3.2.2.1).

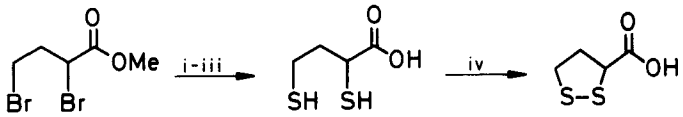
1.5.3. 1,2-Dithiolane-4-carboxylic acid (asparagusic acid) The syntheses of asparagusic acid all employ diethyl bis(hydroxymethyl)malonate as the precursor. The original procedure[22] gave a poor (8.5%) yield and has subsequently been modified. The procedure giving the highest overall yield (31%)[25] is shown in Scheme 6. Alternative methods for the final oxidative cyclization have been reported.[49,74] An alternative strategy involves formation of the 1,2-dithiolane ring before the hydrolysis-decarboxylation step.[36] This sequence apparently gives more readily manageable intermediates, but only an overall yield of 17% due to losses in the final step.



Scheme 6. i: HI/heat, ii: Na_2S_3C/H_2O, iii: 3 M H_2SO_4, iv: DMSO

The l-oxide of asparagusic acid has been prepared from 1,2-dithiolane-4-carboxylic acid with the commonly used oxidants (Table 7, entries 6, 8–11, 14–16).[25,49,75] The *cis:trans* ratio of products is dependent on the choice of the oxidant.[25]

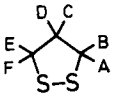
1.5.4. 1,2-Dithiolane-3-carboxylic acid 1,2-Dithiolane-3-carboxylic acid has been synthesized from methyl 2,4-dibromobutanoate (Scheme 7). The original synthesis suffered from a poor yield (12%)[24] because of polymerization. The yield was raised considerably (61%),[76] when care was taken during the liberation of the intermediate dithiol. Use of phenylmethanethiolate ion and subsequent reductive cleavage leads to a comparable yield (66%).[18]



Scheme 7. i: AcSK/EtOH/MeOH, ii: 2 M NaOH/MeOH/H_2O, iii: dil. H_2SO_4, iv: $H_2O_2/FeCl_3$

The acid has been resolved by recrystallization of the cinchonidine salt,[76] the absolute configuration has been established [76–79] and a stereospecific synthesis of (R)-(+)-1,2-dithiolane-3-carboxylic acid starting from L-methionine has been reported.[77,78]

Table 7. Oxidation of 1,2-dithiolanes to 1,2-dithiolane *S*-oxides

Entry	substrate* 	reaction conditions[a]	yield (%)	ref.
Oxidant: $(NH_4)_2S_2O_8$			Product**: 2	
1		1:1, 25°C, 16 h, $EtOH/H_2O$	100[1]	15
2	A = $-(CH_2)_4COOH$	1:1, 25°C, 16 h, $EtOH/H_2O$	100[1]	15
3	A = $-(CH_2)_4COOH$	1:1, 25°C, 24 h, $EtOH/H_2O$ (5:1)	100[1]	177
4	C = -COOH	1:1, 25°C, 20 h, $EtOH/H_2O$ (5:1) 1:1, 25°C, 20 h	100[1]	75
5	C,D = $-(CH_2)_5-$	$EtOH/H_2O$ (5:1) 1:1, 25°C, 20 h	100[1]	75
6	C = -COOH	1:1, 20°C, 5 h, Me_2CO/H_2O (1:1)	78	25
Oxidant: *t*-BuOOH				
7		-	-	523
Oxidant: $PhCO_3H$				
8	C = -COOH	1:1, 0°C, 5 h, CH_2Cl_2	87	25
Oxidant: $NaIO_4$				
9	C = -COOH	1:1, 0°C, 6 h, Me_2CO/H_2O	85	25
Oxidant: *t*-BuOCl				
10	C = -COOH	1:1, −70°C, 1 h, $MeOH/CH_2Cl_2$	80	25
Oxidant: CrO_3				
11	C = -COOH	1:1, 20°C, 4 h, pyridine	83	25
Oxidant: Ce^{4+}				
12		2:1, 25°C, 1 h, H_2O/MeCN (1:4)	100	128
Oxidant: H_2O_2			Product: 2	
13	C = -OH	1:1, 25°C, 48 h, $CHCl_3$/MeCN	28[2,3]	72
14	C = -COOH	1:1, 20°C, 3 h, Me_2CO	65	25
15	C = -COOH	1:1, gentle heat, $\frac{1}{2}$ h, H_2O	63[2]	75
16	C = -COOH	1:1, 5°C. 25°C, 16 h, H_2O	72	49
17	C = D = $-CH_2OH$	1:1, heat, −, H_2O	78[2]	75
18	C,D = $-(CH_2)_5-$	1:1, heat, $2\frac{1}{2}$ h, *i*-PrOH	80[2]	75
19		1:1, 75°C, 1 h. 25°C, 48 h, AcOH	72	51
20	C = -SMe	2:1 (V_2O_5), −20°C. 25°C *t*-BuOH/THF (1:1)	22	93

			Product: 3b	
21	C = D = $-CH_2OH$	2:1, heat, 6 h, H_2O	49[2]	75
22	C,D = $-(CH_2)_5\dot{-}$, 1-oxide	1:1, −, −, *i*-PrOH	-	75
23		5:1 (H^+), 65°C. 25°C, 48 h, AcOH	33	51
			product: 5	
24	1,1-dioxide	4:1 (H^+), 5°C. 25°C, 48 h, dioxane/AcOH (2:1)	8	51
25	C = D = $-CH_2OH$	−, −, −, AcOH	-	3
			product: 6	
26	C,D = $-(CH_2)_5-$	great excess, heat, 3 h, AcOH	-	3
27	C = D = $-CH_2OH$	excess, heat, −, AcOH	33[4]	3
28	C = D = Me	as above	53[4]	4
29	C,D = $-(CH_2SSCH_2)-$		72[4]	5
Oxidant: HCO_3H				
30	A = $-(CH_2)_4COOH$	great excess, 25°C, $1\frac{1}{2}$ h	-	290
Oxidant: *m*-CPBA			product: 3b	
31	C = $-(Me)SO_2$	5:1, 0°C. 25°C, 1 h, CH_2Cl_2/CCl_4	15	93

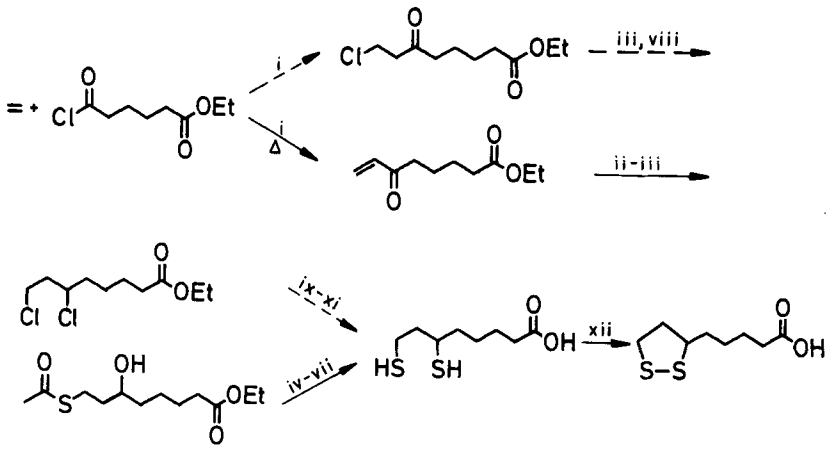
* Substituents different from H are given.
** The oxidation products are numbered in accordance with Scheme 17.
a. Data listed: ratio of oxidant to substrate (catalyst), temp., reaction time and solvent.
1. Determined by UV spectroscopy.
2. Calculated from indirect data.
2. Overall yield from 2-hydroxy-1,3-propanedithiol.
4. Isolated as the barium salt.

1.5.5. 5-(1,2-Dithiolan-3-yl)pentanoic acid (lipoic acid) The literature concerning the synthesis of lipoic acid has been reviewed up to 1969.[18,19,80] Consequently, references before this date are only included in this work as far as they are judged to contain information relevant for the discussion of the later developments.

The structure of lipoic acid was established by synthesis according to Scheme 8 (full arrows).[10,17]

In order to improve the rather poor yield (8%) the procedure has been modified.[16,18,19,35] Treatment of the unsaturated keto ester with H_2/H_2S in the presence of a cobalt sulfide catalyst yielded dihydrolipoic acid upon hydrolysis, and subsequent oxidation afforded lipoic acid (30–39%).[18,19] By careful addition of ethyl adipic acid chloride to ethylene an alternative route to lipoic acid (36%) emerges (Scheme 8, broken arrows).[35] [35]S-Lipoic acid has been prepared by this procedure.[18] Several steps can be by-passed by reaction of the dichloro compound with S_2^{2-}.[18]

(+)- And (−)-lipoic acid have been prepared by resolving the intermediates, ethyl 6,8-dichlorooctanoate[18] and monoethyl 6-(acetylthio)octanedioate,[19] with ephedrin, and by resolution of the thioacetals formed from dihydrolipoic acid and suitable aldoses.[81,82]



Scheme 8. i: $AlCl_3$, ii: AcSH, iii: $NaBH_4$, iv: KOH/H_2O, v: $(NH_2)_2CS/HI$, vi: $NaOH/H_2O$, vii: HCl, viii: $SOCl_2$, ix: $PhCH_2SNa$, x: KOH, xi: Na/NH_3, xii: $O_2/FeCl_3$

Alternatively to the formation of the 8-carbon skeleton of lipoic acid by addition of ethyl adipic acid chloride to ethylene, addition of this acid chloride to acetylene[37] (32% overall yield), reaction of 6-heptenoic acid with formaldehyde[18,19] (20–32% overall yield), peroxidation of 2-(acetoxyethyl)cyclohexanone[19] (19% overall yield), reaction of ethyl 6,6-bis(ethoxy)hexanoate with vinyl ethyl ether[37] (30% overall yield) and telomerization of butadiene[83] (22% overall yield) have been reported.

The absolute configuration of natural (R)-(+)-lipoic acid was proven by synthesis of the (S)-(−)-enantiomer[84] (13%, calculated from indirect data) from (S)-malic acid. A key intermediate in this reaction sequence, (R)-8-(benzyloxy)-6-hydroxy-1-octene, has also been prepared by yeast mediated reduction of isobutyl 5-(benzyloxy)-3-oxopentanoate.[85]

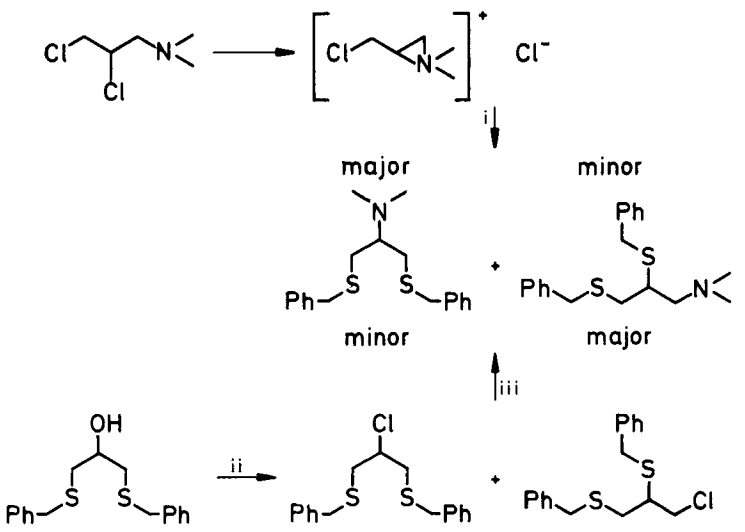
Recently (R)-(+)-lipoic acid has been synthesized in several stereoselective[86,87] and stereospecific[88,89] reaction sequences, starting from (2S,4S)-pentanediol[86] (37%), D-glucose[89] (20.4%, calculated from indirect data), 6-bromo-1-hexene[87] (22%) or 1,3-propanedithiol, using d-menthone as a chiral auxiliary.[88]

The *S*-oxides of lipoic acid have been prepared by oxidation of lipoic acid[15,90] (cf. Table 7).

*1.5.6. 4-(*N,N-*Dimethylamino)-1,2-dithiolane (nereistoxin)* Nereistoxin (32%) has been synthesized from *N,N*-dimethyl-2,3-dichloro-1-propanamine[34] (Scheme 9, top). When the sulfur atoms were introduced prior to the amino group, the yield was very low due to isomerization of the intermediates[33] (Scheme 9, bottom).

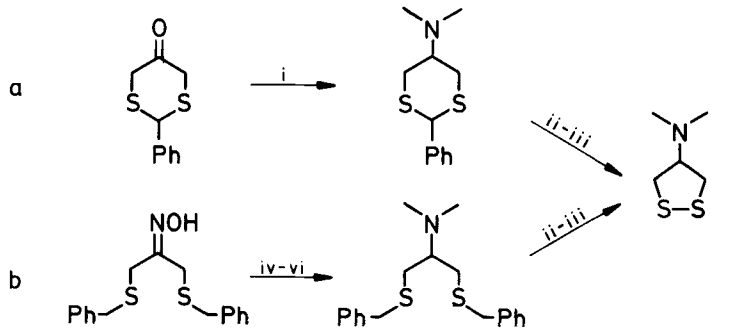
This isomerization also intervenes in the synthesis of the trithiane analog of nereistoxin[91] (Table 2, entry 10).

Nereistoxin has been synthesized without concomitant formation of isomeric by-products using ketone or oxime precursors[52] (Schemes 10a,b). The yield is somewhat lowered by this procedure (10.2 and 24.8%, respectively, calculated from indirect data), but the purification of the product is simplified.



Scheme 9. i: $PhCH_2S^-$, ii: $SOCl_2$, iii: Me_2NH

The syntheses of low-molecular marine toxins, including nereistoxin, have been reviewed.[92a,b]

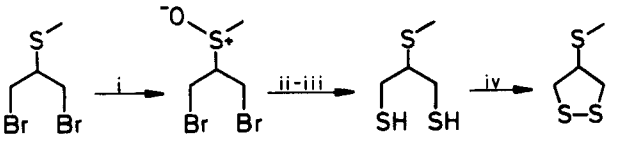


Scheme 10. i: $HCOOH/Mg^{2+}$/DMF, ii: Na/*t*-BuOH, iii: air/$FeCl_3$, iv: $LiAlH_4$, v: HCHO/HCOOH/heat, vi: OH

1.5.7. 4-(Methylthio)-1,2-dithiolane (charatoxin) and 5-(methylthio)-1,2,3-trithiane Charatoxin was originally synthesized from 1,2,3-propanetrithiol.[48] Careful choice of methylation conditions and subsequent chromatographic separation of the reaction mixture yielded the desired intermediate 2-(methylthio)-1,3-propanedithiol (40%). Subsequent oxidation with O_2 or treatment with SCl_2 yielded charatoxin (36%) or 5-(methylthio)-1,2,3-trithiane (19.2%, calculated from indirect data), respectively.

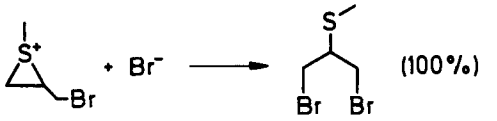
An improved synthesis of charatoxin from 2-(methylthio)-1,3-dibromopropane (76%, determined in solution by NMR spectroscopy) has been reported[93] (Scheme 11). Direct substitution with this substrate, however, leads to isomerization in analogy with nereis-

toxin (Sect. 1.5.6), hence the methylthio group is inactivated by oxidation prior to reaction with trithiocarbonate anion.

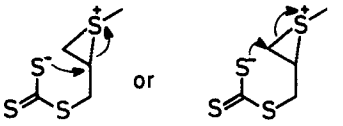


Scheme 11. i: *m*-CPBA, ii: Na_2CS_3, iii: $LiAlH_4$, iv: I_2

The isomerization is surprising, since the starting material is formed in quantitative yield by the bromination of allyl methyl sulfide (Scheme 12) — *i.e.* bromide ion preferentially attacks the primary carbon atom. A possible explanation for this behavior lies in the involvement of a dianionic nucleophile which causes the second sulfur atom to be introduced through a cyclic transition state (Scheme 13). If the five-membered transition state is entropy favored to an extent exceeding the steric restrictions of an attack at a more substituted carbon atom isomerization will occur. It seems possible therefore that the problem could be circumvented by employing a monoanionic nucleophile.



Scheme 12.



Scheme 13.

2. STRUCTURE AND STABILITY

This section mainly deals with the chemical and physical properties of 1,2-dithiolanes, since these differ significantly from those of open-chain disulfides. 1,2-Dithiolanes show a pronounced polymerization tendency, as evident from the previous sections, as well as an enhanced reactivity in radical, electrophilic and nucleophilic reactions.[80] Furthermore, the UV spectra,[e.g. 80] PE spectra[94] and polarographic properties[95–98] of 1,2-dithiolanes show great differences from those of other disulfides.

These differences have been rationalized in terms of the concept of strain of the 1,2-dithiolane ring system. This phenomenon is due to the interplay of steric and electronic effects and still not fully understood.

2.1. Estimations of Strain Energy

The major contributor to the enhanced reactivity of 1,2-dithiolanes is the small dihedral angle, φ (Fig. 1). In the open-chain disulfides, φ assumes values close to 90°[80] and the interaction between adjacent sulfur lone pairs is thereby kept at a minimum.

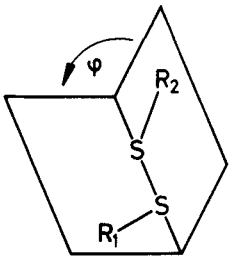


Figure 1. The dihedral angle, φ, defined by the two planes, R_1SS and SSR_2.

In the case of a cyclic disulfide, $(CH_2)_nS_2$, φ can be maintained at 90° only if n is large ($n > 6$)[99,100] and in the unsubstituted 1,2-dithiolane ring ($n = 3$) φ is about 30°,[80,101] hence giving rise to torsional strain. The orbital interactions responsible for this effect have been depicted in terms of different models:

One model describes the normal disulfide in the following manner. When $\varphi = 90°$ the repulsion between the sulfur lone pairs is at a minimum. At the same time electron density is donated from one sulfur atom to empty d-orbitals of the adjacent sulfur atom and vice versa, resulting in some double-bond character of the S–S bond (p_π-d_π-bonding); as φ approaches zero this double bond effect is reduced and the lone pair repulsion increases.

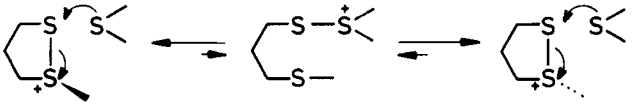
Another model [102,103] is based upon lone pair-lone pair interactions. When $\varphi = 90°$ no interaction between the lone pair orbitals is possible. As φ approaches zero, however, they interact by combining into two molecular orbitals, π^+ and π^-. Since this splitting is not symmetric - π^- is destabilized more than π^+ is stabilized — the S–S bond is weakened as a result of the increasing antibonding contribution as φ goes from 90° to 0°. At the same time the stabilizing n_S-$\sigma^*_{C\text{-}S}$ interactions have their maximum at $\varphi = 90°$ and approach zero with decreasing φ. This contribution works in the same direction as the previous, cf. ref.[104]

Both models lead to the same result, namely a weakened S–S bond in 1,2-dithiolanes compared to open-chain disulfides. As a consequence an increasing bond length with decreasing φ is observed.[94]

The importance of lone pair-lone pair repulsion in governing the characteristics of 1,2-dithiolanes is supported by the fact that any modification of the ring system which removes or reduces this repulsion leads to increased stability. Examples are radical cations (Sect. 2.3.5), *S*-oxides (Sect. 3.2.2) and 1,2-dithiolanium ions.

1,2-Dithiolanium ions have been the subject of thorough investigations[105,106] indicating that 1,2-dithiolanium and 1,2-dithianium compounds, resulting from *S*-methylation of various 1,2-dithiolanes and 1,2-dithiane, are unstrained since the equilibrium quoted in Scheme 14 is strongly in favor of ring formation. The reactivity of 1,2-dithiolanium species is explained in terms of rapid cleavage of the $S\text{–}S^+$ bond by nucleophiles.

The release in torsional strain accomplished by transfer of electron density from the lone pair orbital (n), located at the neutral sulfur atom to σ^* of the adjacent MeS bond



Scheme 14.

in the case of 1,2-dithianyl compounds, is demonstrated by the fact that the chemical shifts of the axial C-3 and C-6 protons are almost equal. Furthermore it was established that methylation of 1,2-dithianes produces only one diastereomer, in which S^+–Me is oriented axially and thereby allows the above-mentioned electron transfer. Calculations indicated the axial position to be more stable than the equatorial by 3.1 kcal/mol.

In contrast to the findings for 1,2-dithianes methylation of 1,2-dithiolanes is unselective. The diastereomers are of comparable energy, which is interpreted in terms of enhanced flexibility allowing the five-membered ring to adopt conformations which counteract destabilizating interactions and at the same time permit axial orientation of S^+–Me. Furthermore, the stability of 1,2-dithiolanium species is demonstrated by the fact that the 1-methyl-1,2-dithiolanium ion could be prepared by methylation of a 1,2-dithiolane polymer.

Values ranging from 3 to 14 kcal/mol have been assigned to the energy barriers to rotation around the S–S bonds.[80] According to more recent work, however, a more reliable range of values seems to be 7–8 kcal/mol when rotation takes place via a *trans* transition state and about 10 kcal/mol in case of rotation via a *cis* transition state.[107,108]

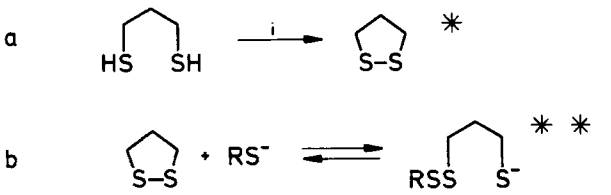
Using this last value and assuming a cos φ dependence of the energy, the torsional contribution to the strain energy in 1,2-dithiolanes can be calculated from $\Delta G_{tor.} = \cos 30° \times 10$ kcal/mol, resulting in $\Delta G_{tor.} = 8$–9 kcal/mol.

Several attempts to obtain a measure of the strain energy of the 1,2-dithiolane ring system have been made, and the results are summarized in the following.

UV Spectroscopic measurements furnished values of 25–30 kcal/mol.[15] Equilibrium measurements of the reaction of 1,2-dithiolane with various thiols led to the values: 6.3 kcal/mol,[15] 5.3 kcal/mol, [109] 4.2 kcal/mol[109] and approximately 4 kcal/mol.[110] Thermochemical measurements of the oxidation of thiols to disulfides resulted in values about 4 kcal/mol.[111] Various structural considerations led to values covering a broad range: 11 kcal/mol,[15] 14–18 kcal/mol[32] 14 kcal/mol[112] and 20–24 kcal/mol.[113,114]

The ΔH values obtained by either thermochemical or equilibrium measurements, falling within the narrow range of 4–6 kcal/mol, are taken as the most reliable when dealing with chemical reactivity since the values obtained from conformational analysis of molecules in the gaseous or crystalline phase do not necessarily reflect the properties of the same molecules in solution.

The reactions in question (Schemes 15a,b) can be expected to proceed with entropy loss (cf. ref.[115]) hence making $\Delta G > \Delta H$ and comparable to the $\Delta G_{tor.}$ given above.



Scheme 15. i: I_2, *: ref.[109], **: refs.[15,107]

2.2. Reactivity

The enhanced reactivity of 1,2-dithiolanes compared to other disulfides is demonstrated by several reaction types, *e.g.* polymerization,[14,15,32,105,106] cleavage of the disulfide bond

by cyanopropyl radicals,[80] cyanide ion[32] and thiolates[109,116] and electrophilic persulfate oxidation to yield thiosulfinates.[15,80] The energy of activation is estimated to be 8.7 kcal/mol[15] for the thermal polymerization of 1,2-dithiolane.

The kinetic acceleration in the cleavage of the disulfide bond by thiolates has been explained in terms of entropies of activation.[80,109,117] The transition state for this reaction is described [80,117] as a complex involving three sulfur atoms separated equally on a straight line. The valence angle of the attacked sulfur atom approaches 90° and the original S–S bond is stretched. The ground state of 1,2-dithiolane (valence angle = 92° and d_{S-S} = Å resembles the transition state more than the ground state of an open-chain disulfide (valence angle = 107° and d_{S-S} = 2.05 Å), hence it is more likely to reach the transition state from the ground state of 1,2-dithiolane — leading to a lower entropy of activation.

This model is used to explain the stability of 1,2-dithiane in various reaction types — *e.g.* cleavage of the S–S bond by cyanide ion,[32] polymerization tendency,[32] reaction with thiolate ions[116] and reaction with methyl trifluoromethanesulfonate.[118] In these cases the relative reactivities of cyclic disulfides with varying ring size were 1,2-dithiolane > 1,2-dithiepane > 1,2-dithiane, although 1,2-dithiane (φ = 60°[119]) must be expected to suffer from some torsional strain. The transition state described above can only be reached from 1,2-dithianes by severe deformation of the carbon valence angles and by giving up the zig-zag conformation of their methylene groups.[80,117]

The enhanced reactivity of 1,2-dithiolanes towards electrophilic reagents is also explained in terms of low energies of activation,[117] and the term "entropy strain" has been introduced to describe the kinetic acceleration in cyclic systems.[118]

The chemistry of 1,2-dithiolanes seems to be governed by energetic conditions resulting from enthalpic and entropic contributions operating in opposite directions.[110,118] The stability is increased with increasing substitution[14,35,111] by a combination of steric and electronic effects not accounted for. These effects, however, are reflected in the spectroscopic properties of the compounds, as evident from the next Sections.

2.3. Physico-Chemical Measurements

2.3.1. UV Spectroscopy

2.3.1.1. Electronic effects The absorption of ultraviolet light by 1,2-dithiolanes occurs at considerably larger wavelengths than those of open-chain disulfides. This red shift is dependent on the dihedral angle, *i.e.* the smaller the angle the larger the shift, as demonstrated by the following examples.

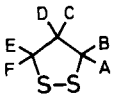
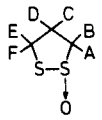
$\lambda_{max}(CH_3SSCH_3)$ = 250 nm, φ = 85°;[119] $\lambda_{max}[(CH_2)_4S_2]$ = 290 nm, φ = 60°[119] and $\lambda_{max}[(CH_2)_3S_2]$ = 330 nm,[15] [φ(1,2-dithiolane-4-carboxylic acid) = 27°].[120] Incorporation of the disulfide bond into polycyclic systems can give very small dihedral angles and the absorption maxima are shifted further towards longer wavelengths; *e.g.* λ_{max} (gliotoxin) = 340 nm, φ = 14°[121] and λ_{max}(1α,5α-epidithioandrostan-3α,17β-diol) = 369 nm, φ = 0°.[122]

The relationship between absorption maxima and dihedral angles has been explained by orbital interactions.[123–125] To a first approximation the S–S bond is considered as an

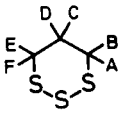
isolated system in which the two lone pairs of each sulfur atom occupy an s- and a p-orbital, respectively. Calculations predict the two highest occupied molecular orbitals to be the bonding and antibonding π-orbitals, resulting from linear combination of two $3p_z$-orbitals. The lowest unoccupied orbital is the antibonding σ^*-orbital located between the sulfur atoms. Excitation therefore consists of transition of an electron from π^- to σ^*. Use of sp^3-hybridized atomic orbitals as the basis orbitals does not alter the general picture.

Since σ^* is symmetric with respect to rotation around the S–S bond its energy is to a first approximation independent of the dihedral angle. π^- is antisymmetric with respect to rotation and its energy therefore dependent of this angle. Hence an increased excitation energy is observed with increasing φ. Since the transition is forbidden by symmetry, low extinction coefficients are observed for 1,2-dithiolanes (Table 8).

Table 8. UV Absorption maxima of naturally occurring 1,2-dithiolanes, 1,2-dithiolane 1-oxides and 1,2,3-trithianes

Entry	compound[1]	$\lambda_{max.}$ (solvent) (nm)	ε	ref.
				
1	C = –OH	236 ($CHCl_3$)	–	30
2	C = –OH	320[a]	–	130
3	C = –OH	347 ($CHCl_3$)	–	72
4	gerrardine, HCl*	336	–	255
5	C = –COOH	330 (EtOH)	–	128
6	C = –COOH	328[a,b] (EtOH)	250	284
7	C = –COOH	330 (EtOH)	126	75
8	A = –COOH	324[a,c] (EtOH)	–	130
9	A = –COOH	328 (EtOH)	–	28
10	A = –COOH	320[a] (EtOH)	130	261[c], 262
11	A = –COOH	325 (EtOH)	162	261
12	A = –COOH	330 (EtOH)	159	524
13	A = $-(CH_2)_4COOH$	333 (EtOH)	–	28
14	A = $-(CH_2)_4COOH$	330	160	119
15	A = $-(CH_2)_4COOH$	332	157	299
16	A = $-(CH_2)_4COOH$	330	150	19
17	A = $-(CH_2)_4COOH$	330 (EtOH)	150	524
18	C = $-NMe_2$	320 (H_2O)	125	33, 34[d]
19	C = $-NMe_2$	320[d] (H_2O)	129	52
20	C = $-NMe_2$	320[d] (H_2O)	144	7
21	C = $-NMe_2$	330 (EtOH)	207	7
22	C = –SMe	332	–	66
				
23	"gerrardine monoxide"*	330 (MeOH)/247 ($CHCl_3$)[a]	148/3700	259
24	"gerrardine dioxide"*	247[a] ($CHCl_3$)	6760	259
25	C = –OH (*trans*)	252[a] (MeOH)	–	130, 258

26	C = -OH (*cis*)	248[a] (MeOH)	-	130, 258
27	C = -COOH	245 (EtOH)	398	75
28	C = -COOH (*cis*)	248[a] (MeOH)	1260	287
29	C = -COOH (*trans*)	248[a] (MeOH)	1260	287
30	A = $-(CH_2)_4COOH$	244 (EtOH)	1025	15
31	A = $-(CH_2)_4COOH$	244 (EtOH)	875	264



32	[e]	264 (MeOH)	1500	40
33	C = -SMe	218, 266	-	66

1. Substituents different from H are given.
* Consult Table 1 for structure.
a. Isolated from natural sources.
b. Data obtained from the butyl ester.
c. Data obtained from brugine*.
d. Data obtained from the hydrogen oxalate.
e. The unsubstituted 1,2,3-trithiane is included as reference.

2.3.1.2. Effects of substitution Introduction of substituents into the 1,2-dithiolane ring influences the UV spectra of these compounds, a matter which has been the subject of much attention.[27,28,39,125-129]

Substitution by electrophilic groups at C-3 and C-5 exerts a minor hypsochromic effect: λ_{max}(1,2-dithiolane-3-carboxylic acid) = 328 nm[28] and λ_{max}(1,2-dithiolane-3,5-dicarboxylic acid) = 326 nm[28] (*vs.* 330 nm for 1,2-dithiolane). The UV spectra of these compounds contain rather intense additional absorption maxima at 280 nm and 250 nm, respectively. These maxima are due to perturbed carbonylic transitions.[125]

A more pronounced hypsochromic effect accompanies substitution by protonized amino groups, *e.g.* λ_{max}(3-aminomethyl-1,2-dithiolane hydrochloride) = 322 nm[28] and λ_{max}(4-aminomethyl-1,2-dithiolane hydrochloride) = 326 nm.[28] Since alkyl groups induce a bathochromic shift (see below), the hypsochromic effect of $-NH_3^+$ is probably larger than indicated by the cited values. Transformation of the free base, $-N(CH_3)_2$, of nereistoxin into the hydrogen oxalate results in a blue shift of 10 nm (Table 8, entries 18–21). The change of solvent may be at least partly responsible for the shift of absorption maximum.

In contrast to normal disulfides, introduction of alkyl groups onto the 1,2-dithiolane ring causes a bathochromic shift: $\lambda_{max}[(CH_3)_2S_2]$ = 255 nm, $\lambda_{max}[(C_2H_5)_2S_2]$ = 252 nmn, $\lambda_{max}[(i\text{-}C_3H_7)_2S_2]$ = 245 nm, $\lambda_{max}[(t\text{-}C_4H_9)_2S_2]$ = 230 nm[125] and λ_{max} (lipoic acid) = 333 nm, λ_{max}(5-methyl-1,2-dithiolane-3-carboxylic acid) = 334 nm, λ_{max}(3,3,5,5-tetramethyl-1,2-dithiolane) = 358 nm.[28] It is not clear whether the blue shift caused by tetramethylation is due to inductive effects or to steric effects resulting in a flattening of the ring. Further examples indicate that steric effects can be responsible for bathochromic shifts — *e.g.* λ_{max}(7-hydroxylipoic acid) = 340 nm and λ_{max}(7-

methyllipoic acid) = 350 nm.[30,80] Since λ_{max}(4,4-dimethyl-1,2-dithiolane) = 331 nm[28] the red shift is not likely to be due to simple summation of inductive effects.

The UV absorption maxima of naturally occurring 1,2-dithiolanes and 1,2,3-trithianes are collected in Table 8. In the case of 4-hydroxy-1,2-dithiolane some controversy exists. Three different values have been reported.[30,72,130]

2.3.2. Vibrational spectroscopy IR and Raman spectroscopy is seldom applied in investigations of 1,2-dithiolanes and 1,2,3-trithianes. In small cyclic systems changes concerning one bond will necessarily influence the remainder of the molecule, resulting in severely coupled oscillations and consequently ambiguous stretching frequencies (cf. ref.[131]). Furthermore, the stretching of S–S bonds, and, to a lesser extent, C–S bonds gives rise to very weak bands in the IR spectrum, and therefore Raman spectroscopy is preferable if stretching frequencies related to sulfur in sulfides, disulfides and related compounds are to be identified.[132]

The Raman spectra of a number of disulfides with dihedral angles varying from 26° to 90° have been investigated.[132] The spectra of all compounds contained strong S–S stretching bands in the region 498–511 cm^{-1}, independent of φ. Furthermore no correlation of the relative intensities of C–S and S–S stretching with the angle < CSS was found.

2.3.3. NMR Spectroscopy Application of NMR spectroscopy to 1,2-dithiolanes and 1,2,3-trithianes has mainly served the purpose of identification and characterization of compounds. No attempts of correlating chemical shift values with other physical parameters have been make.

^1H NMR Spectroscopy is the basis of a conformational analysis of 1,2,3-trithianes[133] resulting in estimated energy barriers of 13.2 kcal/mol and 14.7 kcal/mol for the ring inversion of 1,2,3-trithiane and 5,5-dimethyl-1,2,3-trithiane, respectively. These energy barriers are not sufficient to allow separation of the conformers.

An NMR spectroscopic investigation of the pyramidal inversion of sulfur in platinum complexes bearing a 1,2-dithiolane ligand has been reported.[134 and refs. herein]

^1H and ^{13}C chemical shifts of naturally occurring 1,2-dithiolanes and 1,2,3-trithianes are given in Tables 9 and 10.

2.3.4. Photoelectron spectroscopy Examination of disulfides by PE spectroscopy provides information of conformational character, since the difference between the ionization potentials of the two highest occupied orbitals (π^+ and π^-, Sect. 2.3.1.1) is dependent on the dihedral angle. The energy splitting is maximal when φ is 0° or 180° and minimal when φ is 90°.[104,135,136]

The value of the energy splitting, $\Delta IE = IE_{\pi+} - IE_{\pi-}$, is found to correlate with φ,[94,136,137] by the following equation:

$$\Delta IE = 1.78|\cos \varphi| + 0.13^{94}$$

covering the range: 27° < φ < 110°, for a given S–S distance. The relation is not valid for disulfides with bulky substituents.[138]

When the 1,2-dithiolane ring is part of a bicyclic system (*e.g.* formulas **2** and **3**), φ — determined by X-ray crystallography — is close to zero, and as expected very large

Table 9. ^{1}H NMR Chemical shifts of naturally occurring 1,2-dithiolanes, 1,2-dithiolane 1-oxides and 1,2,3-trithianes.

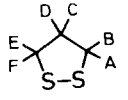
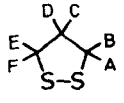
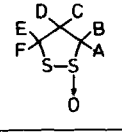
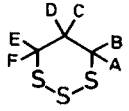
Entry	compound*	solvent/MHz	δ (ppm)	J (Hz)	ref.
					
1	A = B = Me	$CDCl_3$/-	1.55 (s,6,CH_3), 2.09 (t,2,CH_2CMe_2) 3.26 (t,2,CH_2S)	-	68
2	A = B = Me	CCl_4/60,100	1.53 (s,6,CH_3), 2.02 and 3.23 (2m, 2H each, CH_2-CH_2)	-	240
3	A = C = Me (*cis*)	$CDCl_3$/-	1.10 (m,3,CH_3CH), 1.33 (d,3,CH_3CHS), 2.4–3.8 (m,4,ring H)	7	68
4	A = C = Me (*trans*)	$CDCl_3$/-	1.14 (m,3,CH_3CH), 1.4 (d,3,CH_3CHS), 2.5 (m,1,$CHCH_3$), 2.65–3.50 (m,3,CH_2S and CHS)	-	68
5	A = Pr	$CDCl_3$/360	2.44 (m,2,CH_2CH), 3.16 (t,2,CH_2S) 3.60 (t,1,CH)	-	70
6	C = - OH	$CDCl_3$/100	2.41 (broad,1,OH), 3.06 and 3.18 (2dd,$CH_2CHOHCH_2$), 4.90 (m,1,CH)	J_{AX} = 3.5 J_{BX} = 2.2 J_{AB} = 11.5	130
7	C = -COOH	$CDCl_3$/90	3.18–3.68 (m,5,ring H), 11.51 (s,1,COOH)	-	36
8	C = --COOH	C_6D_6/90	2.20–2.53 (m,3), 2.66–2.90 (m,2) 10.90 (s,1,COOH)	-	36
9	C = $-CO_2Me$	C_6D_6/60	2.6–3.2 (m,5,ring H), 3.25 (s,3,OCH_3)	-	268
10	C = $-CO_2Me$[1]	C_6D_6/60	4.75 (dd,2,2^{H1}_{H2} > C(S)-C < $^{H3}_{CO}$), 6.77 (dd,2,2^{H1}_{H2} > C(S)-C < $^{H3}_{CO}$), 7.00 (q,1,CH^3CO) 7.25 (s, 3, OCH_3)	J_{12} = 11.5 J_{13} = 7.2 J_{23} = 5.7	267, 268
11	A = $-CO_2$tropinyl	-/-	2.50 (m,2,CH_2CH), 3.25 (m,2,CH_2S) 4.15 (q,1,CHCO)	J_1 = 4.3 J_2 = 7.5	261
12	A = -COOH	-/-	2.57(m), 3.29(m,), 4.31(q), 9.7(broad)	-	525
13	A = -COOH	$CDCl_3$/60	2.2–2.8 (CH_2CH), 3.1–3.6 (CH_2S), 4.2–4.4 ($CHCOOH$), 10.2 (COOH)	-	524
14	A = $-(CH_2)_4COOH$	$CDCl_3$/60	1.6 (m,6,$3CH_2$), 1.8–2.0 (m,2,CH_2CHS) 2.2–2.6 (m,2,CH_2CO), 2.9–3.3 (t,2,CH_2S), 3.4–3.7 (q,1,CHS), 10.5 (broad,COOH)	-	524, 525
15	A = $-(CH_2)_4COOH$	$CDCl_3$/80,90	1.3–2.8 (m,10,$5CH_2$), 3.10 (t,2,CH_2S), 3.53 (m,1,CHS)	-	89
16	C = $-NMe_2$	D_2O/60	2.97 (s,6,CH_3), 3.53 (d,4,$2CH_2$), 4.40 (qn,1,CH)	-	52[2]

Table 9. Continued.

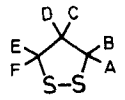
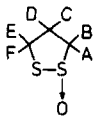
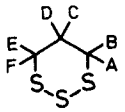
Entry	compound*	solvent/MHz	δ (ppm)	J (Hz)	ref.
					
17	C = -SMe	$CDCl_3$/90	2.25 (s,3), 3.0–3.7 (m,5)	-	66
18	C = -SMe	C_6D_6/90	1.51 (s,3), 2.4–2.8 (m,5)	-	66
19	C = -SMe	C_6D_6/270	1.51 (s,3), 2.6 (m,1), 2.8 (m,4)	-	66
20	C = -SMe	CCl_4/90,360	2.23 (s,3), 2.8–3.8 (m,5)	-	93
21	gerrardine[3]	$CDCl_3$/200	3.26 (dd,2,2CH_AH$_B$CS), 3.31 (dd,2, 2CH$_A$$H_B$CS), 3.52 (dd[a],2,2CHS) 4.60 (m,2,2C*H*OH)	J_{AB} = 11.5 J_{AX} = 2 J_{BX} = 3 [a]J_1 = 2.5 J_2 = 10	256
					
22	C = -OH (*cis*)	-/100	3.44 (dd,1,$^{H2}_{H1}$>C-C<^{OH}), 3.54 (m,2, $^{H5}_{H4}$>C-S<^{OH}), 3.85 (dd,1,$^{H2}_{H1}$>C-C) 5.33 (m,1,*H*^{3}COH)	J_{12} = 11 J_{23} = 6 J_{45} = 13 J_{13} = J_{34} = J_{35} = 5	258
23	C = -OH (*trans*)	-/100	2.92 (dd,1,$^{H4}_{H5}$>C-S^{O}), 3.59 (dd,1, $^{H2}_{H1}$>C-C<^{OH}), 4.05 (dd,1,$^{H4}_{H5}$>C-S^{O}) 4.09 (dd,1,$^{H2}_{H1}$>C-C<^{OH}), 5.42 (m,1,*H*^{3}COH)	J_{12} = 11 J_{13} = 4.3 J_{34} = 3.5 J_{45} = 13	258
24	A = -$(CH_2)_4$COOH	$CDCl_3$/60,90	1.4–2.0 (m), 2.3–2.6 (m), 2.6–2.9 (m) 3.2–3.4 (m), 3.4–3.8 (m)	-	264



25	C = -COOH	$CDCl_3$/-	2.90–3.65 (m)	–	141
26	C = -SMe	$CDCl_3$/270	3.05 (m), 3.24 (m) (total 5H) 2.17 (s,3,CH_3)	–	66

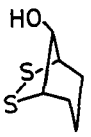
* Substituents different from H are given.
1. $Eu(dpm)_3$ added as shift reagent.
2. Data obtained from the hydrogen oxalate.
3. Consult Table 1 for the structure of gerrardine.

Table 10. ^{13}C NMR Chemical shifts of naturally occurring 1,2-dithiolanes, 1,2-dithiolane 1-oxides and 1,2,3-trithianes

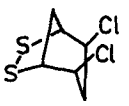
Entry	compound*	solvent	δ (ring carbon) C3	C4 (ppm)	C5	δ (other carbons) (ppm)	ref.
							
1	C = -COOH	$CDCl_3$	41.19	58.39	41.19	178.34 (COOH)	36
2	A = $-(CH_2)_4COOH$	$CDCl_3$	56.00	39.81	38.19		526
3	C = -SMe	-	43.96	50.90	43.96	14.59 (SCH_3)	66
4	gerrardine[1]	$CDCl_3$	65.23	75.7	47.16		256
							
5	"gerrardine monoxide"[1]	$CDCl_3$	64.65	76.04	47.05		259
		$CDCl_3$	68.70[2]	79.23[2]	68.17[2]		259
6	"gerrardine dioxide"[1]	$CDCl_3$	67.86	79.74	68.07		259
							
7	C = -SMe	$CDCl_3$	42.65	45.51	42.65	13.75 (SCH_3)	66

* Substituents different from H are given.
1. Consult Table 1 for structure.
2. δ-values for the oxidized ring.

energy splittings results.[139,140] The ΔIE's of **2** and **3**, respectively, are 2.21 eV and 2.11 eV compared to $\Delta IE_{1,2\text{-dithiolane}} = 1.72$ eV.[94]



(2)



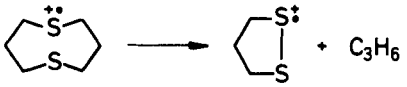
(3)

At this stage it should be kept in mind that measurements of any two different sets of molecular parameters by different physical methods seldom refer to the same state. Therefore the correlation of such quantities is not necessarily straightforward.

It might, however, prove useful to compare data obtained from UV and PE spectroscopy. The UV absorption maxima reflect the energy difference between the ground state and the first excited state (E_{HOMO}-E_{LUMO}), whereas PES provides a measure of all ground-state orbital energies (Figure 2). Hence application of both methods to a given molecule could be indicative of whether an observed spectroscopic change, referring to an appropriate standard molecule, is resulting from changes of ground-state or excited-state energies or both.

The first ionization potentials, the ΔIE's and φ of some naturally occurring 1,2-dithiolanes are collected in Table 11. As a matter of reference the unsubstituted 1,2-dithiolane and dimethyl disulfide are included.

2.3.5. Mass spectrometry The mass spectra of 1,2-dithiolanes are characterized by intense peaks derived from the molecular ions,[42] and in the case of 1,2,3-trithianes the peak corresponding to the 1,2-dithiolanyl radical cation is often dominating the spectra.[141]These results indicate a rather high stability of the 1,2-dithiolanyl radical cations, supported by the fact that dithiacycloalkanes in which the sulfur atoms are separated by three methylene groups, give rise to intense peaks at m/z = 106.[142] For instance, the mass spectrum of 1,5-dithiacyclooctane (Scheme 16) contains a peak at 106, twice the intensity of M^+.



Scheme 16.

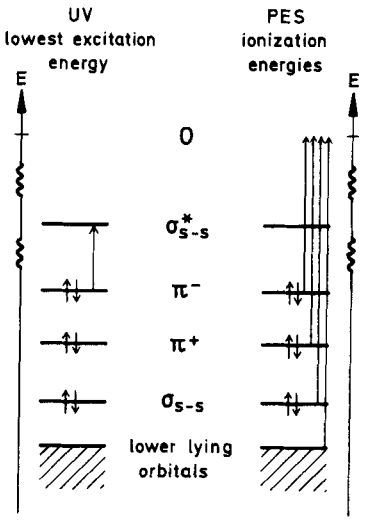


Figure 2. A comparison of the electronic transitions observed in UV and PE spectroscopy.

Table 11. Ionization potentials determined by PE spectroscopy of asparagusic acid and lipoic acid with reference to 1,2-dithiolane and dimethyl disulfide.

Entry	compound	$\Delta IE = IE_2\text{-}IE_1$ (eV)	IE_1 (eV)	IE_2 (eV)	IE_3 (eV)	ref.	ϕ (deg.)	ref.
1	H_3CSSCH_3	0.24	8.97	9.21	-	94	84.7[1]	94
2	1,2-Dithiolane	1.72	8.25	9.97	11.2	94	30	94
3	Lipoic acid	1.79	8.06	9.89	-	94	35[2]	145
4	Asparagusic acid	1.72	8.25	9.97	-	94	26.6[2]	121
5	Asparagusic acid	1.74	8.26	10.00	10.78	36	-	-

1. Calculated value.
2. Determined by X-ray crystallography.

2.3.6. ESR Spectroscopy The stability of 1,2-dithiolanyl radical cations is explained by reduced repulsion between the two sulfur atoms, resulting in a shortened $S\text{-}S^+$ bond and a release of ring strain as φ ($R\text{-}S\text{-}S^+\text{-}R$) approaches zero.[94,143] It is therefore possible to obtain these radical cations in solution. The ESR spectra of the 1,2-dithiolanyl and lipoyl radical cations have been reported.[94,143] The ESR spectrum of the dithiyl radical obtained by photolysis of lipoic acid has also been reported.[144]

2.3.7. X-Ray crystallography X-Ray crystallographic structure determinations of lipoic acid,[145,146] asparagusic acid[119,147,148] and 5-(methylcarbamoyloxy)-1,2,3-trithiane[57,58] have been reported. The latter is included as a representative of the 1,2,3-trithianes, although not naturally occurring.

3. CHEMICAL REACTIONS AND THEIR PRACTICAL APPLICATIONS

3.1. Electrochemistry

3.1.1. Electrochemical investigations The electrochemical properties of 1,2-dithiolanes are a controversial subject. Polarographic investigations have been employed in the structure elucidation of lipoic acid[11] which was characterized as a disulfide, since these were the only known sulfur compounds reducible at the dripping mercury electode.

This property has been put to use in comparing the stabilities of cyclic disulfides of varying ring size with open-chain disulfides.[95,127,149] The 1,2-dithiolanes were the only compounds which were reduced reversibly, and their half-wave potentials were appreciably less negative than those of the larger rings (Table 12). The reaction appears to consist of a two-electron reduction leading to formation of 1,3-dithiols. A detailed mechanism of as well the anodic as the cathodic processes has been proposed[150-153] and it was established that the measured potentials result from chemical reactions of the sulfur compounds with mercury, as evidenced by the results not being reproducible at a platinum electrode.[153] This finding is supported by results obtained for lipoic acid, which was found to be reducible only at the mercury electrode, but not so at either platinum, glassy carbon, tungsten or zink electrodes.[154] This work indicates, however, that only one reduction equivalent is consumed in cathodic as well as chemical reduction (Sect. 3.2.1) of lipoic acid.

Table 12. Half-wave potentials versus S.C.E. of various disulfides at different pH.

Entry	compound	$-E_{1/2}$(V) pH: 1	2.2	4	4.6	7	9.2	13	ref.
1	1,2-Dithiepane-3,7-dicarboxylic acid	–	0.92	–	–	–	–	–	128
2	1,2-Dithiane-3,6-dicarboxylic acid	–	0.76	–	–	–	–	–	128
3	1,2-Dithiolane-3,5-dicarboxylic acid	–	0.33	–	0.44	–	–	–	128
4	1,2-Dithiolane-3-carboxylic acid	–	0.37	–	–	–	–	–	128
5	Asparagusic acid	–	0.37	–	–	0.65[1]	0.76[1]	–	128
6	Asparagusic acid	0.21	–	0.38	–	0.58	–	0.8	98
7	Lipoic acid	0.22	–	0.39	–	0.56	0.69	0.83	98
8	Lipoic acid	–	0.36	–	–	–	–	–	128
9	Lipoic acid	–	–	0.4[2]	–	0.598	–	–	97
10	Nereistoxin	0.24	–	0.44	–	0.63	0.72	0.82	98

1. Deformed wave.
2. Determined from indirect data.

Furthermore, lipoic acid is not reduced in aqueous solution at either platinum or glassy carbon electrodes, whereas dihydrolipoic acid and lipoic acid can be anodically oxidized.[155,156] Likewise it is reported that lipoic acid is not reduced at a gold electrode in aqueous solution and only at -1.92 V in acetonitrile.[157]The latter result is ascribed to chemical reduction at the metal surface by H_2, formed from traces of water in the solvent.

In contrast to these findings, cyclic voltammetry of the ferrous complex of dihydrolipoic acid is reported to give rise to a reversible peak (-0.65 V) at a gold electrode.[158]

Finally, lipoamide is reported to be quantitatively reduced at a tungsten electrode (-1 V). The active reducing agent is believed to be tungsten hydrides located on the electrode surface.[159]

The extreme resistance of lipoic acid and other 1,2-dithiolanes towards electrochemical reduction has been explained in the following terms[157]: Electrochemical reactions proceed via successive one-electron transfers. Since the primarily produced 1,2-dithiolane radical anion is of extremely unfavorable energy, it will immediately react chemically and thereby prevent transfer of a second electron.

The radical anions of lipoic acid and lipoamide have, however, been observed under special conditions.[160-162] A polargraphic investigation including lipoic acid, asparagusic acid and nereistoxin has been reported.[98] For a thorough discussion of the electrochemical methods see the cited literature and additional refs.[96,97,163,164]

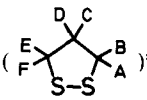
3.1.2. Practical applications of electrochemical methods An electrochemical method of detection and counting of bacteria in water and thereby of measuring bacterial response to pharmaceuticals has been developed.[165-172] Bacteria are grown on a minimal medium supplied with lipoic acid. The redox potential as a function of time is monitored by use of a combined gold/reference electrode. During bacterial growth lipoic acid is reduced to dihydrolipoic acid, which causes a potential drop at the gold electrode.

Cathodic stripping voltammetry with a mercury pool electrode has been employed in

the detection of low concentrations of lipoic acid (detection limit: 10^{-8} M). Several compounds which react with mercury can be determined.[173] Likewise, polarographic procedures determining the content of lipoic acid in multi-component drug preparations,[174,175] and the hydrolysis rates of nereistoxin and cartap [1,3-bis(carbamoylthio)-2-*N*,*N*-dimethylaminopropane],[176] have been reported.

3.2. *Redox Reactions*

3.2.1. Reduction 1,2-Dithiolanes may be reduced by the general methods[21b] applicable

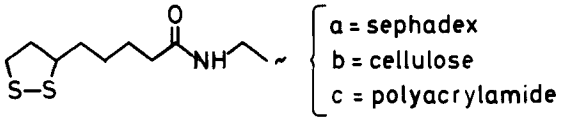
Table 13. Reduction of 1,2-dithiolanes ()* to the corresponding 1,3-dithiols.

Entry	substrate	reaction conditions	yield (%)	ref.
Reductant: Zn/HCl				
1		conc. HCl, 10 min.	100	15
Reductant: Zn/NH_4OH				
2	C = -COOH	4 M NH_3	-	22
3	A = E = -COOH	4 M NH_3	90	519
4	C = -COOH	2 M NH_3, 20°C, 1 h	90[1]	25
Reductant: Na/NH_3				
5	C,D = $-(CH_2)_5-$	-	93	3
6	C = $-CH_2OH$	-	88	3
7	C,D = $-(CH_2SSCH_2)-$	-	80	18
Reductant: H_2				
8	C = D = $-CH_2OH$	Co-polysulfide catalysis, 56–140 atm, 115°C	71	18
Reductant: $NaBH_4$				
9	A = $-(CH_2)_4COOH$	0.25 M $NaHCO_3$, max 5°C, $\frac{1}{2}$ h	91	214
10	A = $-(CH_2)_4COOH$	10-fold excess of $NaBH_4$, $EtOH/H_2O$ (1:1), 25°C, 4 h	37[2]	213
Reductant: vitamin B_{12s} (Co^+)				
11	A = $-(CH_2)_4COOH$	2-fold excess of Co(I)-alanin, H_2O, under N_2	100	527

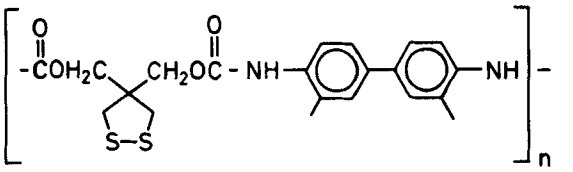
* Substituents different from H are given.
1. Calculated from indirect data.
2. Calculated after subsequent acetylation.

Table 14. Reduction of polymers (I, II) and a model compound (III), containing the 1,2-dithiolane structure, to yield the corresponding 1,3-dithiols*.

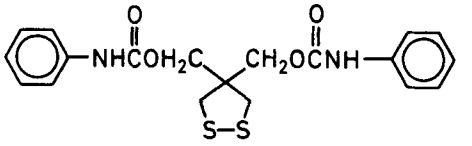
I:



II:



III:



Entry	substrate	reaction conditions	yield (%)	ref.
Reductant: $NaBH_4$				
1	I-a	The substrate is swollen in water.	100	188
2	I-b	50 mg $NaBH_4$ per mg gel is added.	100	188
3	I-c		100	188
4	II	The substrate is added to a 3-fold	50	191
5	III	excess of $NaBH_4$ in MeOH. 0–5°C under N_2. Reaction time: 1 h (II), $\frac{1}{2}$ h (III).	95	191
Reductant: $LiAlH_4$				
6	II	$LiAlH_4$ (6:1) is added to the substrate	90	191
7	III	in dry THF. 0–5°C under N_2. 1 h	92	191
Reductant: NaH				
8	II	The substrate in dioxane is added	6	191
9	III	NaH under N_2. 4 h at 15–25°C.	4	191
10	II	As above. Solvent: DMSO	88	191
11	III		94	191
Reductant: $(n\text{-Bu})_3P$				
12	II	Phosphine and substrate (20:1) in dioxane/H_2O (9:1) react 4 h at 15–25°C under N_2.	11	191
13	II	As above. Solvent: THF/H_2O (9:1).	29	191
14	II	As above. Solvent: MeOH/H_2O (9:1).	35	191
15	II	As above. Reaction time: 10 h.	56	191

* These 1,3-dithiols are all capable of reducing oxidized glutathione quantitatively.

to open-chain disulfides — *i.e.* cathodic reduction and reduction by metal–acid combinations, dissolving metals and complex metal hydrides (Table 13). Table 14 contains data on reduction of polymer-bound 1,2-dithiolanes. These are discussed further in Sect. 3.2.3.1.

The redox reactions of 1,2-dithianes are biochemically interesting because of the involvement of lipoic acid in the oxidative decarboxylation of α-keto acids (Sect. 4.6.1.2.1). During this series of enzymatic reactions hydrogen atoms are transferred from pyruvic acid to FAD via the lipoic acid/dihydrolipoic acid couple.

A recent thorough investigation[109] of the thiol-disulfide interchange reaction affords relative reduction potentials of forty thiol-disulfide couples, including several 1,3-dithiol/1,2-dithiolane couples.

The products of reduction of 1,2-dithiolanes are 1,3-dithiols (Table 13); however, these 1,3-dithiols are not necessarily the primary products. An investigation[154] of the reduction of lipoic acid, cathodically or with Zn/HCl, Mg/HCl or Zn amalgam/HCl showed that only one reduction equivalent was consumed in every case. Hence the primary product of the one-electron reduction was believed to be either the 8-SH, 6-thiyl radical or the 6-SH, 8-thiyl radical of lipoic acid (in acid solution).

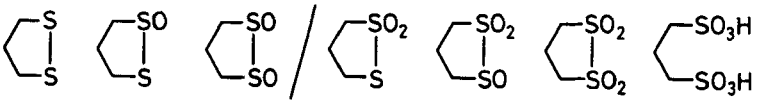
Trisulfides normally lead to the same reduction products as disulfides,[21b] and no indications of a different behavior of 1,2,3-trithianes are found in the literature. However, potassium sulfide, which causes reduction of open-chain disulfides to thiols,[21b] has been reported to effect desulfurization of a 1,2,3-trithiane[5] (Sect. 1.3, Scheme 3), but it is possible that the product 1,2-dithiolane results from autoxidation of an intermediate dithiol.

3.2.2. Oxidation

3.2.2.1 Oxidation procedures 1,2-Dithiolanes are susceptible to oxidation by the same oxidizing agents as those used for the oxidation of open-chain disulfides.[21c,d] Since oxidation of 1,2-dithiolanes is accompanied by a release of ring strain (Sect. 2.1) the reaction is more easily effected than in the case of open-chain disulfides.[94,177]

The one-electron oxidation of 1,2-dithiolanes, producing 1,2-dithiolanyl radical cations (see also Sect. 2.3.5) likewise proceeds more easily than in the case of open-chain disulfides.[176] This fact is clearly demonstrated by comparison of the related redox potentials, which proves a greater oxidizing power of $(CH_3\text{–}S\text{–}S\text{–}CH_3)^{+\circ}$ compared to $(\text{lipoic acid})^{+\circ}$ and $(\text{lipoate anion})^{+\circ}$.[178]

The theoretically possible oxidized products of 1,2-dithiolanes are listed in Scheme 17. Table 7 compiles the products of oxidation encountered in the literature (by reference to Scheme 17), together with the oxidizing agents employed and the substrates with which they are used.



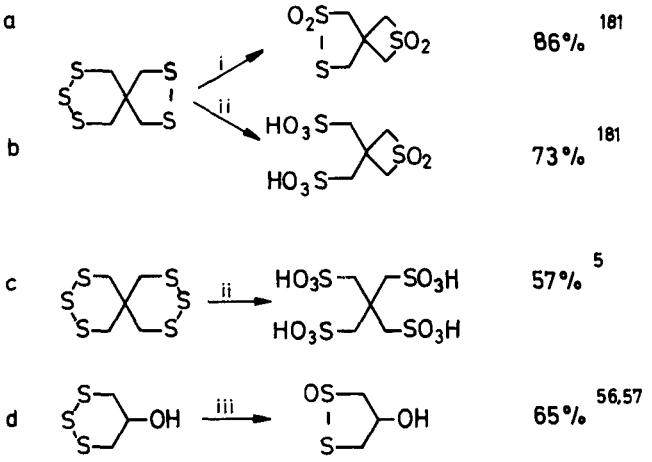
1 2 3a 3b 4 5 6

Scheme 17.

By careful oxidation of 4,4-bis(hydroxymethyl)-1,2-dithiolane with potassium permanganate under various conditions[75] the presence of all oxidation products (Scheme 17, **2–6**) was indicated by the titration curve.

The oxidation products Scheme 17 **3a** and **4** have not been isolated.[179] In the case of open-chain disulfides sulfinyl sulfones (RSO_2SOR) have been isolated,[180] and *vic*-disulfoxides are believed to occur as transient reaction intermediates.[180–182]

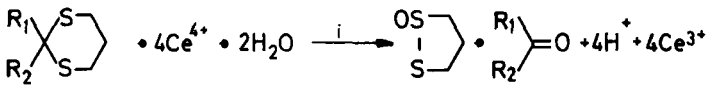
1,2,3-Trithianes yield oxidation products derived from 1,2-dithiolanes (Schemes 18 a–d) — *i.e.* oxidation proceeds, with loss of sulfur, to 1,2-dithiolane oxides and sulfonic acids.



Scheme 18. i: $PhCO_3H/CHCl_3$, ii: $H_2O_2/AcOH$, iii: excess *m*-CPBA

No oxides of 1,2,3-trithianes are encountered in the literature although the two possible monoxides of 1,5-dihydro-2,3,4-benzotrithiepin[40] and various oxides of open-chain trisulfides[181 and refs. herein] have been isolated.

A useful alternative synthesis of 1,2-dithiolane 1-oxide is avialable.[184] Oxidation of 1,3-dithianes with Ce^{4+}, followed by hydrolysis leads to formation of the product (Scheme 19) without involvement of the unstable 1,2-dithiolane.

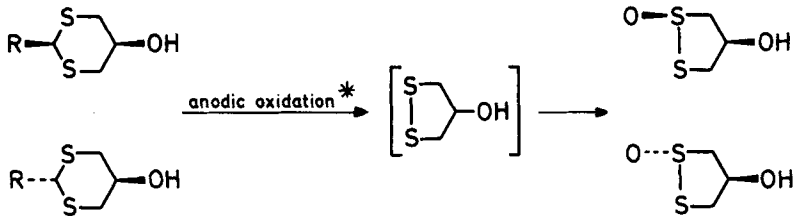


Scheme 19. i: $MeCN/H_2O$, 25°C

A related procedure[73] consists of anodic oxidation of substituted 1,3-dithianes, yielding 1,2-dithiolane oxides. The brugierols have been synthesized by this method (Scheme 20, see also Sect. 1.5.2).

3.2.2.2. Physico-chemical properties of 1,2-dithiolane oxides The UV absorption maxima at 330 nm and the reversibility of polarographic reduction at the mercury electrode are not found for the oxidized derivatives of 1,2-dithiolanes.

1,2-Dithiolane monoxides absorb ultraviolet light in the vicinity of 250 nm (Table 8).



Scheme 20. *: +0.9 V in $MeCN/H_2O$, R = 4-$MeOC_6H_4$- (yield: 62%, *cis:trans* = 55:45) or R = *t*-Bu (yield: 33–41%, *cis:trans* = 3:2)

1,2-Dithiolane 1,1-dioxide shows an absorption maximum at 263 nm compared to λ_{max} (1,2-dithiane 1,1-dioxide) = 244 nm and λ_{max}(1,2-dithiepane 1,1-dioxide) = 240 nm.[51] This order of decreasing absorption wavelength is valid also for the parent rings.[127]

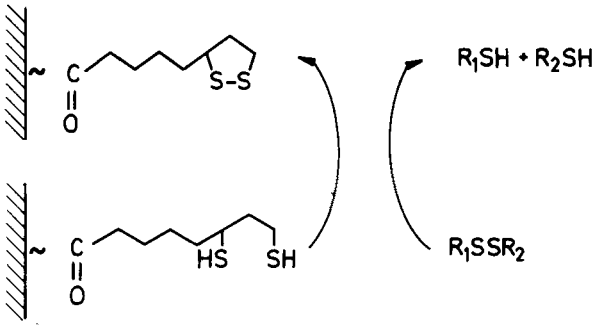
The half-wave reduction potentials of 1,2-dithiolane monoxides are more negative than those of the parent rings,[75] consistent with a stronger S–S bond in the oxides. The polarographic properties of nereistoxin monoxide have been reported.[185,186] In the case of di- and tetroxides of 5-, 6- and 7-membered cyclic disulfides, however, the oxidized compounds are more easily reduced than the parent ring; the 5-membered ring being the most reactive of each group.[187] The authors stress the point that the results do not necessarily provide a relative order of reactivities of the S–S, S–SO_2 and SO_2–SO_2 bonds, since such a comparison implies identical reaction paths. Among the di- and tetrasulfides, respectively, the order of reactivity was 5 > 7 > 6 (referring to ring size) in the cathodic reduction and also for the hydrolysis rates and reactions with nucleophiles (cf. Sect. 2.2). Hence it was concluded that the factors governing the stability of 1,2-dithiolanes are operative in the oxidized derivatives as well. The di- and tetroxides seem to be more stable than the parent ring towards reaction with thiols and polymerization, but less so towards polarographic reduction and hydrolysis.[187]

3.2.3. Practical applications of redox reactions

3.2.3.1. Polymer-bound reductants Mercapto compounds, *e.g.* mercaptoethanol and thioglycolic acid, have frequently been employed in the reduction of disulfide bridges in proteins.[188] However, these reductants must be applied in great excess since the equilibrium constants of such thiol-disulfide exchange reactions are close to unity. The use of dithiols forming cyclic disulfides upon oxidation, *e.g.* dithiothreitol and dithioerythritol, favors completion of the reaction,[189] but purification difficulties are often encountered in this procedure. These facts prompted the use of polymer-bound dihydrolipoic acid as an insoluble reducing agent,[188] acting according to Scheme 21. The oxidized reagent is subsequently removed by filtration or centrifugation and re-reduced for further use (Table 14).

N-Propyldihydrolipoamide, supported by a glass bead matrix,[190] and 1,2-dithiolanes other than lipoic acid derivatives[191] have been found to act similarly.

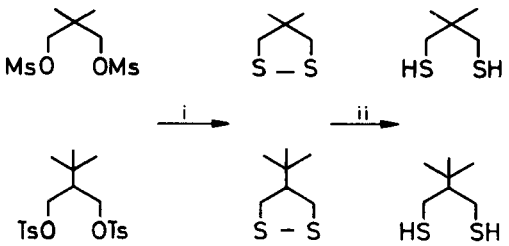
Furthermore, ferrous complexes of dihydrolipoic acid — either free or polymer supported — are capable of reducing, or act as cayalysts for $NaBH_4$ reduction, of various functionalities.[158,192–196]



Scheme 21.

The most refined utilization of polymer-bound lipoic acid derivatives consists of the incorporation of lipoamide into a polymeric membrane, *i.e.* poly(γ-methyl-D-glutamate), thereby producing a membrane capable of carrying electrons from the reductant to the substrate located on opposite sides of the membrane by successive reductions and reoxidations of the 1,2-dithiolane ring.[197,198]

3.2.3.2. Synthesis of sterically hindered 1,3-dithiols The formation of 1,3-dithiols with bulky substituents from the corresponding dielectrophilic substrates suffers from steric hindrance of the incoming sulfur nucleophile. In these cases, therefore, it may be advantageous to use dianionic nucleophiles (cf. Sect. 1.1.1), which are reactive due to the double negative charge and which facilitate disubstitution by the proximity of the reaction centers (anchimeric effect). The use of disulfide ion leads to 1,2-dithiolanes (Sect. 1.1) which are subsequently reduced to 1,3-dithiols. By use of this procedure, 2,2-dimethyl-1,3-propanedithiol (61%) and 2-(*t*-butyl)-1,3-propanedithiol (70%) have been prepared in good yield[199] (Scheme 22).



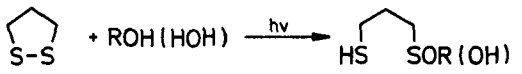
Scheme 22. i: $Na_2S/S_8(\sim S_2^{2-})$/DMF ii: $LiAlH_4$

3.2.3.3. Miscellaneous uses of 1,2-dithiolane derivatives Polymer-bound lipoic acid derivatives have been employed in the purification of enzymes, *e.g.* lipoamide dehydrogenase[200] and lipoate dehydrogenase,[201] and biotin antibodies.[202] Various dihydrolipoyl reagents are reported to participate in some very efficient esterolytic systems.[203] 1,2-Dithiolane 1-oxide derivatives have been used as starting materials in a patented reaction sequence leading to thiosulfonic acid derivatives.[204]

3.3. *Photochemistry*

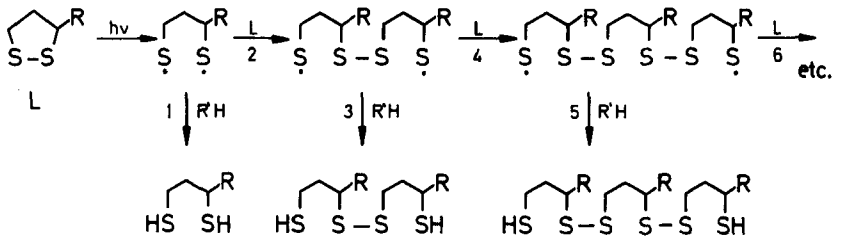
3.3.1. Photolysis During photolysis of 1,2-dithiolane and lipoic acid[15,205-207] it was observed that the yellow color and the UV absorption maxima at 330 nm, characteristic of the 1,2-dithiolane ring, disappeared concomitantly with precipitation of polymeric material.

Upon photolysis in acidic ethanol, however, no polymer was formed although the 1,2-dithiolane ring has disappeared. This result was interpreted in terms of an initial formation of mercapto sulfenic acids (or esters), since only one thiol group was liberated from each 1,2-dithiolane unit (Scheme 23). The primary products were not stable, as verified by a change with time in the UV spectra of the photolysis mixture.



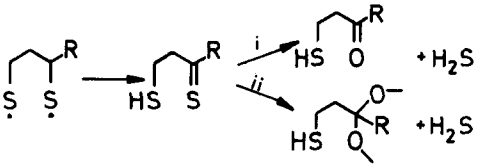
Scheme 23.

Later it was established[208] that the choice of solvent plays a major role in determining the identity — and the rate of formation — of products. The photolysis mixtures of lipoic acid in a series of solvents were analyzed, and some of the products were isolated by TLC. The major products turned out to be oligomers of lipoic acid. The chain length of these oligomers is determined by the availability of hydrogen atoms in the solvent. From these results a mechanism of the photolysis of lipoic acid was postulated (Scheme 24). In the case of solvents bearing easily detachable hydrogen atoms (*e.g.* 2-propanol) route 1 is predominating, whereas solvents lacking this property (*e.g.* hydrocarbons) allow the formation of larger oligomers (routes 2,3,4,... etc.) before the reaction is terminated by hydrogen abstraction.



Scheme 24. R = $-(CH_2)_4COOH$, R'H = solvent

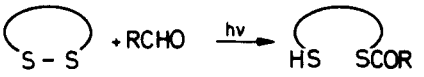
Lipoic acid oligomers are not the sole products of photolysis. When primary alcohols are used as solvents H_2S is liberated, indicating rupture of at least some C–S bonds. An alternative mechanism was proposed (Scheme 25) to account for this result.



Scheme 25. i: H_2O, ii: MeOH

3.3.2. Photooxidation The photooxidation of 1,2-dithiolane, as a model for lipoic acid, has been investigated.[15,205-207] Under normal conditions 1,2-dithiolane is not oxidized by O_2, however photooxidation in the presence of a sensitizer, *e.g.* zinc tetraphenylporphin, proceeds smoothly. One oxygen atom is consumed per molecule of 1,2-dithiolane, hence the product is believed to be 1,2-dithiolane monoxide.

3.3.3. Reductive acylation The photolysis of various open-chain and cyclic disulfides in aldehyde solutions to give *S*-acylated products has been investigated.[209-211] The reactivities of the two substrate categories were comparable, except in the case of unsymmetrically substituted compounds with branched α-carbons. The photolysis of symmetrical substrates (Scheme 26) occurred without concomitant formation of by-products.

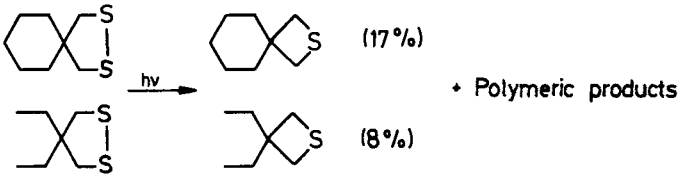


Scheme 26.

In the case of unsymmetrically substituted disulfides two products are possible. The reaction shows a high degree of regioselectivity, yielding the product acylated at the least hindered sulfur atom. This selectivity is pronounced in the case of cyclic substrates, leading to regiospecific reactions from certain substrates. *E.g.* acetylation of 3-methyl-1,2-dithiane yields 96% 5-(acetylthio)-2-mercaptopentane.[211] The reaction of lipoic acid is less specific, yielding 78% of the least hindered product—*i.e.* 8-(acetylthio)dihydrolipoic acid.[209] However, it is more selective than the analogous acylation, effected by acid derivatives (Sect. 3.4.1).

The photochemical acylation with aldehydes is believed to proceed via a photoinduced radical chain mechanism[211] since comparable results are obtained by initiation with azobis(isobutyronitrile). Open-chain disulfides, which do not absorb light in the wavelength region ($\lambda > 330$ nm) used, are also susceptible to photoacylation. It is assumed that the reaction is initiated by excitation of the aldehyde ($n \rightarrow \sigma^*$ transition).

3.3.4. Photosulfurization and desulfurization Beside the polymeric products formed by photolysis of 1,2-dithiolanes in inert solvents (Sect. 3.3.1) considerable amounts of photodesulfurized products (thietanes) are produced (Scheme 27, solvent: pentane) [211] By photolysis in better hydrogen-donating solvents, *e.g.* 2-propanol, the yield of thietane is reduced to less than 1%.



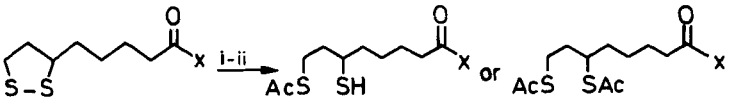
Scheme 27.

The reverse reaction, *i.e.* sulfurization of a thietane to produce a 1,2-dithiolane by reaction with sulfur atoms under photochemical conditions, has also been described.[212]

3.4. Further Chemical Reactions

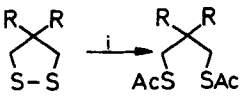
3.4.1. Reductive acylation

3.4.1.1. Acylation of 1,2-dithiolanes The preparation of 8-*S*-acyllipoic acid derivatives under photochemical conditions was described in Sect. 3.3.3. Acylation can also be accomplished by action of electrophilic reagents on 1,3-dithiols. Mono- and diacylated derivatives of lipoic acid have been prepared by the use of one or two equivalents of acetic acid anhydride, respectively (Scheme 28).[213]



Scheme 28. X = -OH, $-NH_2$, i: $NaBH_4/EtOH/H_2O$, ii: Ac_2O/Et_3N

By the use of n-Bu_3P the reaction can be performed in a single step. Simultaneously the yield of diacylated products is raised from 50% to 67%[191,213] (Scheme 29).



Scheme 29. R = $PhNHCO_2CH_2$-, i: n-$Bu_3P/Ac_2O/AcOEt$

The reaction of acid halides with thiols tends to give low yields of monoacylated product.[214] However, utilization of carboxylic acids as less electrophilic acylation agents in the above-mentioned single-step reaction leads to appreciable amounts of monoacylated lipoamide[215] (Scheme 30).

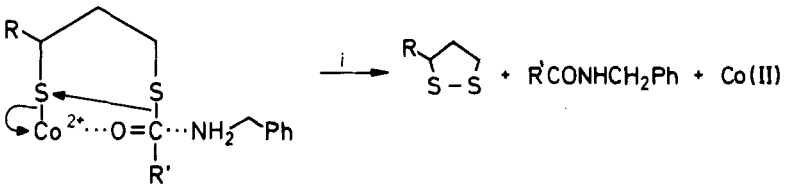
Scheme 30. R = $-(CH_2)_4COHN_2$, R' = Me, $-CH_2COOH$, 4-MeO-C_6H_4-, 4-NO_2-C_6H_4-, L-$C_6H_5CH_2OCONHCH(Me)$-, i: MeCN/60°C

By chemical monoacylation of lipoic acid derivatives 8-*S*-acyl derivatives are obtained whereas the product of enzymatic acylation is believed to be the 6-*S*-acyl isomer, although the actual structure is a matter of some controversy.[216,217] NMR Spectroscopic measurements establish that rapid transfer of acyl groups between the 8-*S* and the 6-*S* position, leading to an equilibrated reaction mixture, is possible.[218]

An analogous reaction — *i.e.* cleavage of the S–S bond in lipoic acid by nucleophiles — is found to be regioselective (preferring the 8–*S* position), but not regiospecific.[219]

3.4.1.2. Practical applications of acylated 1,2-dithiolane derivatives In analogy with the reductive properties of polymer-bound dihydrolipoic acid (Sect. 3.2.3.1) acylated dihydrolipoic acid and analogous compounds are capable of transferring acyl groups to amines and certain alcohols and thiols.[213,215,220–224] Mono- as well as diacyl derivatives of

1,2-dithiolanes are able to acylate various amines. In the presence of certain oxidizing catalysts rate enhancement as well as quantitative transacylation from the monoacylated species is achieved. No such effects were observed in the case of diacylated compounds.[221]

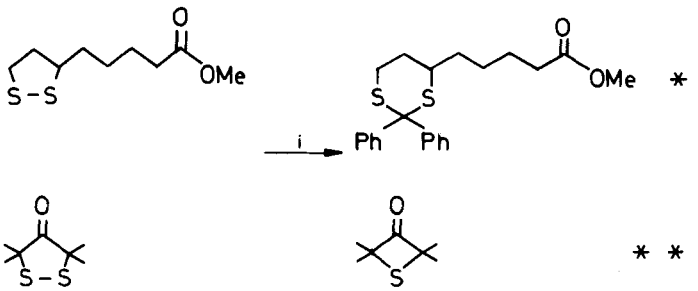


Scheme 31. R = -$(CH_2)_4CONHCH_2Ph$, R' = 4-NO_2-C_6H_4-, i: O_2

Further investigations[221,223,224] proved that several oxidizing catalysts (Ag^+, O_2/Co^{2+}, O_2/flavin and bis(4-pyridyl) disulfide) exert this action, and a mechanism (Scheme 31) for the O_2/Co^{2+}-catalyzed acylation of benzylamine has been proposed.[221]

Incorporation of the 1,2-dithiolane structure into various polymers[213] provides an insoluble acylating agent, capable of acyl transfer to amines, and to a lesser extent, alcohols and thiols. Both mono- and diacyl derivatives are active.

3.4.2. Reaction with carbenes The reaction of carbenes with cyclic disulfides follows a different course from the analogous reaction with open-chain disulfides.[225] Dialkyl disulfides react with carbenes to afford predominantly the corresponding sulfur ylide, which by subsequent cyclic β-elimination gives an olefin. In the case of cyclic disulfides a quantitative S–S insertion reaction occurs, except for severely hindered substrates, which give rise to desulfurized products. The two alternative reaction routes are exemplified in Scheme 32. Diaryl disulfides react inefficiently with carbenes, yielding the S–S insertion product.



Scheme 32. i: N_2CPh_2/CuCl, *: 100%, **: 28%

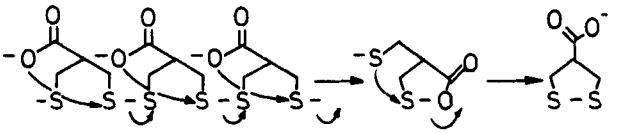
3.4.3. Polymerization-depolymerization

3.4.3.1. Formation of (S–S)-polymers As evident from the previous Sections one of the most characteristic features of 1,2-dithiolanes is their tendency to polymerize. Polymerization is effected in several ways, *i.e.* by the influence of light, thermally in solution or under the influence of oxidizing agents.

The polymerization tendency of 1,2-dithiolanes under electrophilic conditions has been explained in terms of initial formation of 1,2-dithiolanium ions, followed by monomer-induced ring opening.[105,106] This process is reversible, since methyl 1,2-dithiolanium ions are formed by methylation of 1,2-dithiolane polymer (Sect. 2.1).

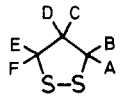
Heating neat 1,2-dithiolanes may also cause polymerization. This property has been described for 1,2-dithiolane-3-carboxylic acid,[24] asparagusic acid[36,74] and for lipoic acid,[226] all of which are transformed from yellow crystals into colorless glasses upon heating.

Polymers of 1,2-dithiolanes have been depolymerized under various conditions (Table 15). Vacuum sublimation,[226] heating in inert solvents[36,51,227] or in alkaline solutions[15,36,74,226] and treatment with solid iodine[99] have been reported to effect this transformation. The following mechanism (Scheme 33) of the base-catalyzed depolymerization of asparagusic acid has been proposed.[74]



Scheme 33.

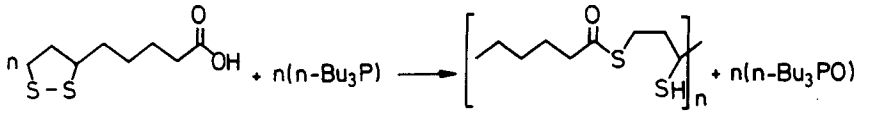
3.4.3.2 Condensation Presence of functionalities besides the disulfide unit makes it possible to form polymers in addition to the (S–S)-polymers. Treatment of lipoic acid with n-Bu_3P[228] results in polycondensation, leading to a thioester polymer (Scheme 34)

Table 15. Depolymerization of (S-S)-polymers to yield 1,2-dithiolanes ()*.

Entry	product	reaction conditions	yield (%)	ref.
1		Steam distillation with strong NaOH or KOH.	–	15
2		80–85°C for 7 days.	90–100[1]	51
3		75°C in MeCN.	80[1]	51
4		Reaction with a 2-fold excess of solid I_2.	72	99
5		160°C in paraffin or nujol.	–	227
		Dissolution in aqueous buffer:		
6	C = -COOH	pH 12–7.3	100[1]	74
7	C = -COOH	pH 6.4 (2 min.)	80[1]	74
8	C = -COOH	pH 5.75 (15 min.)	80[1]	74
9	C = -COOH	pH 4.22 (2–14 days)	25–80[1]	74
10	C = -COOH	Dissolution in sat. aq. $NaHCO_3$.	–	36
11	A = $-(CH_2)_4COOH$	Vacuum subl. (120°C)	46	226
12	A = $-(CH_2)_4COOH$	Heating on steam bath in 0.5 M NaOH.	70	226
13	A = $-(CH_2)_4COOH$	4 mmol NaOH per mmol lipoyl units. (EtOH, 25°C, 30 min.)	77	226

* Substituents different from H are given.
1. Determined by UV spectroscopy.

whereas the reaction of lipoic acid with cyclic phosphonites spontaneously produces an alternating, phosphorus-containing copolymer.[229]



Scheme 34.

3.4.3.3. Dimerization The existence of a cyclic dimer of 1,2-dithiolane was proposed already at the turn of the century;[1,2] however, the isolation and characterization of this compound was carried out only recently.[230] 1,2,6,7-Tetrathiadecane was synthesized by I_2 oxidation of 1,3-propanedithiol in the presence of NEt_3 under conditions of extreme dilution. The product was isolated by TLC.

The analogous dimer of lipoic acid is believed to be formed by radiolysis of lipoic acid in aqueous media, although disulfides are expected to yield sulfonic acids upon radiolysis.[231] In the case of lipoic acid only minor amounts of oxidized products and thiols were produced. The radiolysis mixture was separated by gel filtration. A fraction (25%, MW = 320) believed to be the cyclic dimer of lipoic acid (MW = 412) was isolated.

3.4.4. Metal complexes 1,2-Dithiolanes possess a pronounced affinity towards mercury (see Sect. 3.1.1.), and several 1,2-dithiolanes have been isolated as stable Hg^{2+} adducts (cf. Tables 2, 3 and 6).

Attempts have been made to prepare analogous complexes with other metal ions,[232] but this property seems to be a distinctive feature of Hg^{2+}. Lipoic acid forms a stable, crystalline Hg^{2+} adduct, whereas thermal or photolytic cleavage of the S–S bond is necessary to accomplish complexation with Zn^{2+}, Co^{2+}, Ca^{2+} or Pb^{2+}. Dihydrolipoic acid forms stable adducts with all of these cations. Accordingly, lipoic acid exhibits only minor depressant activity in a copper-molybdenum separation procedure.[233] In contradiction with this finding, lipoic acid is found to be capable of extraction of Cu^{2+} from an aqueous phase to benzene.[234] The carboxylate group seems to be the site of coordination in this case.

For a further discussion of the metal coordinating properties of 1,2-dithiolanes — with special emphasis on the biochemically important lipoic acid — cf. refs.[235-238]

Finally the synthesis of a $Fe_2(CO)_6$ derivative of lipoic acid has been reported.[239]

4. BIOLOGICAL PROPERTIES OF NATURALLY OCCURRING 1,2-DITHIOLANES AND 1,2,3-TRITHIANES

4.1. Alkyl Substituted Compounds

4.1.1. Natural occurrence The alkyl substituted 1,2-dithiolanes are constituents of the anal gland secretions of small carnivores belonging to the genus *Mustela*. Their identification is usually based upon comparison with synthetic material (Sect. 1.5.1).

3,3-Dimethyl-1,2-dithiolane has been detected in the anal sac of the ferret (*M. putorius*

forma *furo*),[68] the mink (*M. vison*),[240-242*,244] the weasel (*M. nivalis*)[245] and the polecat (*M. putorius*).[244,245] 3,3-Dimethyl-1,2-dithiolane accompanied by 4,4-dimethyl-1,2,3-trithiane is also present in fox (*Vulpes vulpes*) droppings.[246]

3-Propyl-1,2-dithiolane is present in the anal sacs of the male stoat (*M. erminea*),[67] the ferret,[68] the polecat[245] and the weasel.[245]

3-Ethyl-1,2-dithiolane has been found only in the anal gland secret of the female stoat,[67] thereby being both species and sex specific. The possible occurrence of this compound in the mink has been discussed[241] without comparison with synthetic material.

3,4-Dimethyl-1,2-dithiolane (both isomers) are present in the ferret,[68] in the closely related species, the polecat, and in the weasel.[245]

The possible natural occurrence of two additional alkyl substituted compounds, 3-isopropyl-1,2-dithiolane and 3,5-dimethyl-1,2-dithiolane, has been discussed.[245]

A comparison of the content of volatile material in the anal sacs of carnivores (Mustelidae) has been performed.[243] The results are reproduced in Table 16. It is evident from the Table that species belonging to the same genus show very little variation in the composition of the anal gland secretion. No similarity is found by comparison of the anal sac contents from differrent genera belonging to the same family. (Cf. ref.[241])

3,3-Dimethyl-1,2-dithiolane and 3,3-dimethyl-4-oxo-1,2-dithiolane have also been identified in roasted coffee.[247] Their presence in this case, however, may arise from oxidation of the corresponding dithiols during the roasting. Cf. ref.[248] for a thorough discussion of this issue.

4.1.2. Biosynthesis The biosynthetic origin of the alkyl substituted sulfur compounds has not been fully accounted for. It has been suggested that the formation of the compounds characteristic of the mink, *e.g.* 2,2-dimethylthietane, 3,3-dimethyl-1,2-dithiolane[249,250] and diisopentyl disulfide,[244] may proceed through isoprenoid precursors. Isoprenic units are not present in the compounds containing longer alkyl chains, and these compounds are believed to be derived from straight-chain fatty acids.[67]

4.1.3. Natural biological functions The contents of the anal sacs of mustelides serve the purpose of scent marking, *i.e.* chemical communication.[242] Each species belonging to Mustela shows a unique array of components in the anal gland secretion, and for each individual the components are present in a specific ratio. Sex specific compositions are rare; the only examples described are the occurrence of 3-ethyl-1,2-dithiolane in the female stoat[67], 3-propyl-1,2-dithiolane in the male stoat (Sect. 4.1.1) and a change in the composition of the anal gland secret of the female ferret during estrus.[68]

Mustelides use their anal gland secretion for territorial marking[242] and presumably to a lesser extent for defense, since frightened individuals empty their anal sacs.[243] Defense is believed to be a secondary function because of the relatively low content of highly volatile material. Animals for which defense is the primary function, *e.g.* the striped skunk, show a much greater preference for volatile components.[251]

* The assigned structure was 1,2-dithiacycloheptane, based on considerations of the degradation pattern in the mass spectrum. Later[243] this view was modified and, by comparison with ref.,[241] it is evident that the correct structure is 3,3-dimethyl-1,2-dithiolane.

Table 16. Distribution of compounds in the anal gland secretion of species of Mustelidae*

Compound	*Mustela ermenia*	*Mustela nivalis*	*Mustela vison*	*Mustela putorius*	*Mustela putorius* forma *furo*	*Martes foina*	*Martes martes*	*Lutra lutra*	*Meles meles*
2-Methylthietane	$+^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	
2,2-Dimethylthietane	$+^{a}$		$\oplus^{a,d}$	$+^{b,d}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2,4-Dimethylthietane	$-^{a,b}$	$+^{a}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2,3-Dimethylthietane (*trans*)	$+^{a}$	$+^{a,b}$		$+^{a,b}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2,3-Dimethylthietane (*cis*)	$+^{b}$	$+^{b}$		$+^{b}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2-Ethylthietane	$+^{a,b}$	$+^{b}$	$+^{a}$	$+^{b}$	$+^{b}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2-Propylthietane (isomer of)	$+^{a}$			$\oplus^{a}$		$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2-Propylthietane (isomer of)	$+^{a}$			$-^{a}$		$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2-Propylthietane	$\oplus^{a,b}$	$+^{b}$		$+^{b}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
2-Pentylthietane	$+^{a,b}$			$+^{b}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
3,3-Dimethyl-1,2-dithiolane		$\oplus^{a,b}$	$+^{a,d}$	$+^{a,b,d}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
3,4-Dimethyl-1,2-dithiolane	$-^{b}$	$+^{b}$	$-^{b}$	$+^{b}$	$+^{b,c}$	$-^{b}$	$-^{b}$	$-^{b}$	
3-Ethyl-1,2-dithiolane	$+^{a}$					$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
3-Propyl-1,2-dithiolane	$+^{a,b}$	$+^{b}$		$+^{b}$	$+^{b,c}$	$-^{a,b}$	$-^{a,b}$	$-^{a,b}$	$-^{a}$
Indole	$+^{a,d}$	$+^{a}$	$+^{a}$	$+^{a,d}$	$+^{c}$		$-^{a}$	$-^{a}$	$-^{a}$
2-Aminoacetophenone	$+^{a}$	$-^{a}$	$-^{a}$	$-^{a}$	$-^{a}$		$-^{a}$	$-^{a}$	$-^{a}$
Benzaldehyde	$-^{a}$	$-^{a}$	$-^{a}$	$-^{a}$	$-^{a}$		$\oplus^{a}$	$-^{a}$	$-^{a}$
Butyric acid	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$+^{b}$	$+^{b}$	$+^{b}$	
Isobutyric acid	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$+^{b}$	$-^{b}$	$+^{b}$	
2-Methylbutyric acid	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$+^{b}$	$-^{b}$	$+^{b}$	
Isovaleric acid	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$-^{b}$	$+^{b}$	$+^{b}$	$+^{b}$	
Trimethylamine	$+^{b}$	$-^{b}$	$-^{b}$	$+^{b}$	$+^{b}$				
Quinoline				$+^{b}$	$+^{c}$				
Diisopentyl disulfide			$+^{d}$	$+^{d}$					

a. ref.[243]
b. ref.[245]
c. ref.[68]
d. ref.[244]
* Predominant compounds are encircled^{a};
$-^{a}$ designates not present in amounts exceeding 10 ng per animal;
$-^{b}$, $-^{c}$, $-^{d}$ designates not observed;
empty spaces designates no data recorded.

4.1.4. Practical applications Chemical communication through scent markers is not restricted to occur between individuals of the same species. Indications of communication between totally different species have been found.[246,252]

The feeding of hares (*Lepus americanus*) is influenced by specific components present in the anal gland secret of various mustelides. The hares, which are prey to the stoat, do not feed on pine seedlings treated with 3-propyl-1,2-dithiolane of 2,2-dimethylthietane, both present in the anal gland secret of the stoat.[252] This finding implies a potential use of these alkyl substituted compounds in crop protection.

The stress inducing effect of 3,3-dimethyl-1,2-dithiolane and 4,4-dimethyl-1,2,3-trithiane, present in fox droppings, on rats, constitutes an additional example of interspecies communication.[246]

4.2. 4-Hydroxy-1,2-dithiolane and Derivatives

4.2.1. 4-Hydroxy-1,2-dithiolane The title compound was extracted from the stem and bark of *Bruguiera cylindrica*, a member of the mangrove family (Rhizophoraceae).[129] These plants are remarkable for their content of various cyclic disulfides.[249]

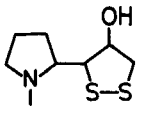
Apart from the syntheses mentioned (Sect. 1.5.2) the literature concerning 4-hydroxy-1,2-dithiolane is sparse. No investigations of the biosynthetic origin nor the natural biological function have been reported.

The biological activities of a number of compounds related to the brugierols (*syn*- and *anti*-4-hydroxy-1,2-dithiolane 1-oxide) against nine common pests have been examined.[58] The tests included the *N*-methyl- and *N*-ethyl carbamates of 4-hydroxy-1,2-dithiolane (but not the free hydroxy compound). The mortality of house mosquitoes, exposed to these compounds, was 90% and 80%, respectively.

Another work[253] on the insecticidal activity of 1,2-dithiolanyl pyrrolidine carbamates shows that the *N*-methyl carbamate of 1-methyl-2-(4-hydroxy-1,2-dithiolan-3-yl)pyrrolidine controls *Chilo suppressalis* larvae.

4.2.2. 1-Methyl-2,5-bis(4-hydroxy-1,2-dithiolan-3-yl)pyrrol (gerrardine) Gerrardine was originally isolated from an extract of twigs and leaves of *Cassipourea gerrardii*.[254,255] Later its presence in the bark of *Cassipourea guianensis* — another Rhizophoraceae family member — was established.[256] It has been established by an X-ray analysis that the two 1,2-dithiolanyl groups are *trans* and that the absolute configuration at C-4 of both disulfide rings is S.[257]

Two additional alkaloids were isolated from *Cassipourea gerrardii*[254,255]: gerrardamine, $C_8H_{15}NOS_2$, and gerrardoline, $C_8H_{15}NO_2S_2$, described as a gum and an amorphous substance (m.p. 60°C), respectively. No structures were assigned to these compounds. Formulas **4** and **5** (or perhaps polymers hereof) might be suggested for these substances:



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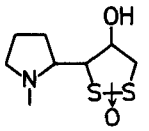


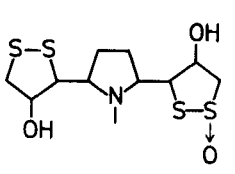
(5)

Gerrardine exhibits bactericidal effects on *Salmonella* and *Stigella* strains,[254] *Candida albicans* TA., *E. coli* NIHJ JC-2, *E. coli* 0–111 and *Klebsiella pneumoniae* DT.[256] No evidence concerning the natural biological function of gerrardine has been recorded.

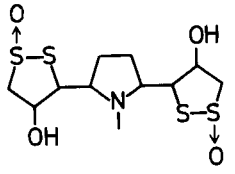
4.2.3. cis- *and* trans-*4-Hydroxy-1,2-dithiolane 1-oxide (the brugierols)* The brugierols were extracted from the stem and bark of *Bruguiera conjugata* (Rhizophoraceae).[258] The *cis* and *trans* isomers were named isobrugierol and brugierol, respectively, inconsistent with the nomenclature used by the same authors in later work.[58]

The biological tests mentioned in Sect. 4.2.1 included methyl and ethyl carbamates of the brugeriols. Only the methyl carbamate of *cis*-brugierol showed significant insecticidal activity. *cis*-Brugierol exhibited antibacterial activities against hyochi bacillus, dysentery bacillus, typhoid bacillus, cholera bacillus and pneumobacillus.[58]

4.2.4. Oxidized derivatives of gerrardine In addition to gerrardine two alkaloids have been isolated from *Cassipourea guianensis*:[259] 1-methyl-2-(1-oxo-4-hydroxy-1,2-dithiolan-3-yl)-5-(4-hydroxy-1,2-dithiolan-3-yl)pyrrolidine ("gerrardine monoxide", **6**) and 1-methyl-2,5-bis(1-oxo-4-hydroxy-1,2-dithiolan-3-yl)pyrrolidine ("gerrardine dioxide", **7**). These compounds are not believed to be artefacts, since control experiments show that gerrardine is not oxidized under the conditions applied during extraction and isolation. No biological effects of these compounds have been recorded.



(6)



(7)

4.3. 1,2-Dithiolane-3-carboxylic Acid

4.3.1. Natural occurrence Esterification of 1,2-dithiolane-3-carboxylic acid with the amino alcohol tropine leads to brugine, a representative of a wide variety of naturally occurring tropine alkaloids.[260] The absolute configuration around C-3 is generally agreed to be S.[76–79,260,261] Brugine has been isolated from *Bruguiera sexangula*,[261] *B. exaristata*[262] and *B. cylindrica*,[263] all members of Rhizophoraceae.

1,2-Dithiolane-3-carboxylic acid also occurs naturally as a metabolite of lipoic acid.[264]

4.3.2. Biological activity Extracts of the bark of *B. sexangula* have been applied in antitumor tests, and were found active against two types of tumors. The identity of the active components was not established and, furthermore, the alkaloids are toxic.[262]

4.4. 1,2-Dithiolane-4-carboxylic Acid (Asparagusic Acid) and Derivatives

4.4.1. Asparagusic acid

4.4.1.1. Natural occurrence Asparagusic acid was originally isolated in polymeric form

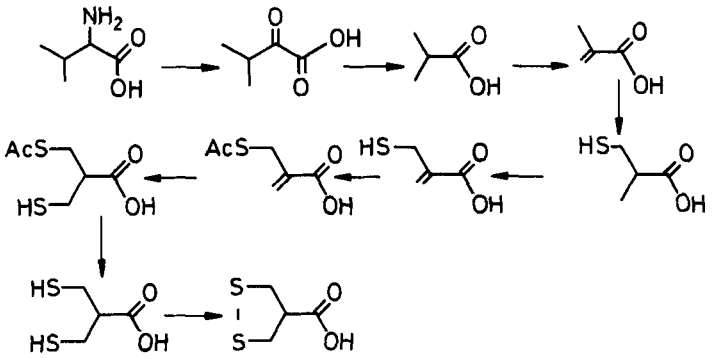
from asparagus.[265] The identification was based upon the fact that reduction of the isolated material yielded 2-(mercaptomethyl)-3-mercaptopropanoic acid. This structure was later verified by synthesis.[266] Subsequently the monomeric acid was isolated from etiolated asparagus shoots (*Asparagus officinalis* L.).[267,268]

The content of asparagusic acid is highest in the growth region of the asparagus shoots (as are the contents of the asparagusate dehydrogenase and the lipoate dehydrogenase enzyme complexes), and the acid concentration is larger in green than in etiolated shoots (the opposite holds for the enzyme complexes). Asparagusic acid is present in all asparagus species investigated.[269]

4.4.1.2. Natural biological function It has been suggested that asparagusic acid participates in enzymatic reactions of asparagus by acting as the substrate of asparagusate dehydrogenase, thereby stimulating pyruvate oxidation, and by inhibiting lipoate dehydrogenase. The enzyme systems, asparagusate dehydrogenase I and II, are believed to play a regulatory role in the oxidative decarboxylation of α-keto acids, which takes place in the asparagus mitochondria.[270-275]

4.4.1.3. Biosynthesis The biosynthetic pathway to asparagusic acid has been investigated.[276-279] Radioactive labeling experiments proved isobutyric acid to be the precursor for asparagusic acid. It was indicated that the isobutyric acid originates from the amino acid valine,[276] and that at least one sulfur atom is donated by the amino acid cysteine.[279]

The proposed biosynthetic route is given in Scheme 35. All intermediates were detected in the sulfur-enriched part of an asparagus homogenate by GC–MS analyses.



Scheme 35.

4.4.1.4. Practical applications Asparagusic acid has been referred to as a plant growth inhibitor because of its effect on the growth of roots and hypocotyl of barley, rice, radish, rape, lettuce, carrot and barnyard grass seedlings.[267,268,280] The relationship between the disulfide group in asparagusic acid and malformin and the inhibitory action of these compounds on plants have been reviewed.[281,282]

The following additional biological effects of asparagusic acid and derivatives have been recorded: Asparagusic acid, dihydroasparagusic acid and *S*-acetyldihydroasparagusic acid are found to stimulate growth and pyruvate oxidation of *Streptococcus faecalis* 10C1.[283]

An aqueous solution (50 ppm) of asparagusic acid totally inhibits the hatching of second-stage larvae of *Heterodera rostochiensis* and *H. glycines*, and exerts a nematocidal effect (% mortality given in parentheses) on second-stage larvae of *H. rostochiensis* (99), *Meloidogyne hapla* (92) as well as larvae and adults of *Pratylenchus penetrana* (82) and *P. curvitatus* (82).[284]

Asparagusic acid exhibits a cytostactic effect on skin fibroblasts,[285] and *N*-(1,2-dithiolane-4-carbonyl)-L-proline and its esters inhibit hypertension induced by angiotensin I.[286]

4.4.2. Asparagusic acid S-*oxide* The *syn*- and *anti*-*S*-oxides of asparagusic acid have been isolated from etiolated asparagus, *A. officinalis* L.[287] They exhibit a concentration-dependent growth regulatory effect on the roots and hypocotyl of a number of higher plants (Sect. 4.4.1.4). Their activity is pronounced at 6.7×10^{-4} M, but only slight at 6.7×10^{-6} M. The asparagusic acid *S*-oxides stimulate the oxidation of pyruvate in *S. faecalis* (Sect. 4.4.1.4), although to a lesser extent than asparagusic acid itself.[283]

Several derivatives of the formula 4-X-1,2-dithiolane 1-oxide, X = COOH, COOR, $CONR^1R^2$ and alkyl, have been reported to stimulate the antibody formation as well as the antigen-dependent cell division of lymphocytes.[288]

4.4.3. Miscellaneous derivatives of asparagusic acid Dihydroasparagusic acid, *S*-acetyldihydroasparagusic acid[267,268] and a number of esters of asparagusic acid[276] have been reported to be naturally occurring. A gas chromatographic examination of an asparagus homogenate indicated that methyl asparagusate is in fact the major sulfur-containing constituent of asparagus.[276] The recorded biological activities of these compounds are presented in Sect. 4.4.1.4.

4.4.4. 1,2,3-Trithiane-5-carboxylic acid 1,2,3-Trithiane-5-carboxylic acid was detected by GC–MS analysis of an asparagus homogenate (Sect. 4.4.1.3).[276] However, the trithiane was believed to be an artefact, formed from asparagusic acid upon heating.[289] Later 1,2,3-trithiane-5-carboxylic acid was isolated from asparagus (*A. officinalis L.*)[141] by a procedure which did not involve temperatures exceeding 40 °C. Hence this compound was considered to be naturally occurring.

4.6. 5-(1,2-Dithiolan-3-yl)pentanoic Acid (Lipoic Acid) and Derivatives

4.6.1. Lipoic acid

4.6.1.1. Natural occurrence Lipoic acid is the most widely spread and the most thoroughly investigated representative of the 1,2-dithiolanes. Its presence has been detected in a great number of living organisms, ranging from microorganisms to plants and animals,[290] mainly in protein-bound form by amide formation with the ε-amino group in a non-terminal lysine residue*.[290,291,292] The amino acid sequence of this *N*-lipoyllysine residue has recently been determined.[293]

* In the biological literature the amide formed by lipoic acid and this lysine residue is described as lipoamide.

Prior to the identification of lipoic acid its activity was noticed during work with various microorganisms. A variety of names were applied to describe the active factor — *e.g.* protogen A, "acetate replacing factor" and "pyruvate oxidation factor".[294] In 1951 a pure, crystalline compound of high biological activity was isolated from beef liver.[9] This compound was named α-lipoic acid. Later the structure of lipoic acid was elucidated[10,11] and the name 6,8-thioctic acid was proposed.[10] The acknowledged trivial name (The American Society of Biological Chemists, 1955) is, however, lipoic acid.

During the following years the presence of lipoic acid (or the pyruvate dehydrogenase multienzyme complex) was demonstrated in bacteria, yeast, higher plants, pigeon breast musculature, skin fibroblasts and several mammalian organs.[295]

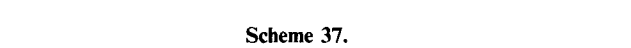
4.6.1.2. Natural biological functions

4.6.1.2.1. Oxidative decarboxylation Lipoic acid possesses several biological properties the earliest recognized and most thoroughly investigated quality of which is its role in the oxidative decarboxylation of α-keto acids. From a chemical point of view this process is analogous to the reductive acylation and acyl group transfer described in Sect. 3.4.1.

The biochemical processes are well understood and are described in common textbooks.[296] More recent literature does not alter the general views on the role of lipoic acid.[297,298] The total biochemical process consists in the transfer of acetyl groups from pyruvate to coenzyme A concomitantly with reduction of NAD^+ (Scheme 36).

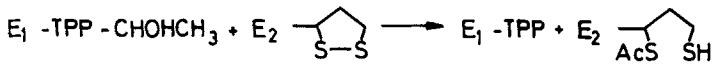
Scheme 36.

This process requires three enzymes and five coenzymes (including lipoic acid*), organized in a multienzyme complex and is divided into five distinct steps (Schemes 37–41).



Scheme 37.

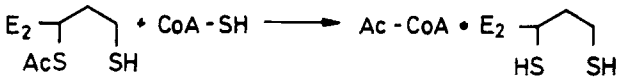
The first step is catalyzed by pyruvate dehydrogenase (E_1) with thiamine pyrophosphate (TPP) as prosthetic group. An "activated acetyl group" is formed and transferred to the 6-*S* atom of lipoic acid in the second step (Scheme 38).



Scheme 38.

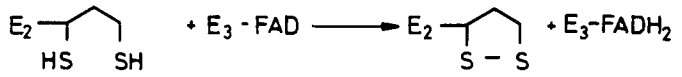
This reaction is catalyzed by lipoate acetyltransferase (or dihydrolipoyl transacetylase, E_2). The third step consists of transfer of the acetyl group from lipoic acid to the mercapto group of coenzyme A (Scheme 39).

* Lipoic acid is termed a coenzyme although it is covalently bound to protein by amide formation. Some authors ascribe the status of a vitamin to lipoic acid (vitamin N).[174]



Scheme 39.

In the fourth step the disulfide bond of lipoic acid is restored by action of lipoamide dehydrogenase (or dihydrolipoyl dehydrogenase, E_3) and the corresponding coenzyme, flavine adenine dinucleotide (Scheme 40).



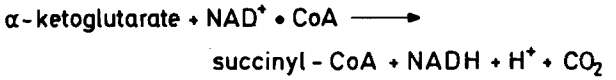
Scheme 40.

Finally, $FADH_2$ is reoxidized by NAD^+ (Scheme 41).

Scheme 41.

The above reaction sequences are essential for the entry of carbohydrates (via pyruvate) into Krebs' cycle. The responsible multi-enzyme complex, including two additional regulatory enzymes: pyruvate dehydrogenase kinase and pyruvate dehydrogenase phosphatase, has been thoroughly examined; for the results and conclusions of these investigations see the original literature.[12,19,80,117,207,290,294,295,299-322]

The oxidation of α-ketoglutaric acid to succinyl-CoA (Scheme 42) is analogous to the oxidation of pyruvic acid.[290,296] The reaction sequence is part of Krebs' cycle and is governed by the α-ketoglutarate dehydrogenase complex, assisted by the coenzymes thiamin pyrophosphate, lipoic acid, CoA, FAD and NAD^+ This multienzyme complex bears much resemblance to the pyruvate dehydrogenase complex and has likewise been thoroughly investigated.[314-320,323-326]

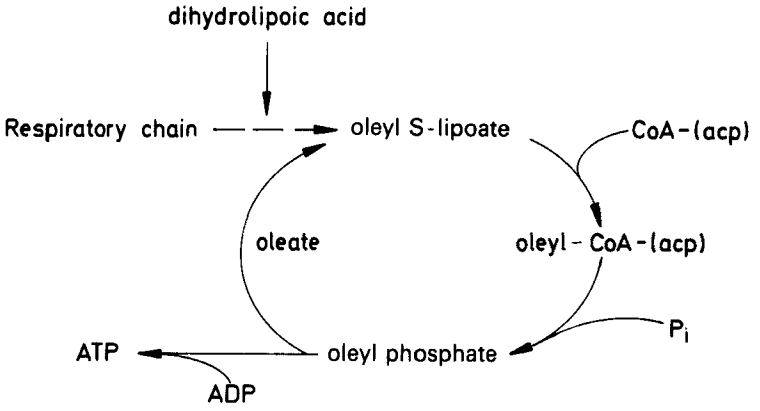


Scheme 42.

4.6.1.2.2. Oxidative phosphorylation Lipoic acid is believed to play a central role in oxidative phosphorylation.[327-335] The exact nature of the reactions involved in unknown, but it is believed that lipoic acid (in non-protein bound form) acts by transfer of acyl (oleyl) groups and is capable of connecting the respiratory chain* to the ATP synthetase complex through the oleyl cycle (Scheme 43).

4.6.1.2.3. Photosynthesis The role of lipoic acid in photosynthesis was the subject of great attention in the 1950's.[15,205,337-342] Lipoic acid was first supposed to be directly involved in the act of quantum conversion, *i.e.* the formation of molecular oxygen from

* Independent work[336] shows that dihydrolipoic acid is capable of reducing cytochrome c.



Scheme 43. acp: acyl carrier protein

water by transfer of excitation energy from excited chlorophyll, resulting in cleavage of the disulfide bond with formation of a dithiyl radical. This diradical was thought to react with water yielding a mercaptosulfinic acid (cf. Sect. 3.3.1.) which by further transformations yielded dihydrolipoic acid and oxygen.

A modified theory does not involve lipoic acid in O_2 formation; instead lipoic acid is believed to function as an electron carrier between chlorophyll and NADP, and thereby to constitute a link between the photosynthetic apparatus and the photosynthetic carbon cycle, Krebs' cycle and the cytochrome system. This mode of action of lipoic acid is consistent with its function in oxidative decarboxylation (Sect. 4.6.1.2.1.), oxidative phosphorylation (Sect. 4.6.1.2.2.), which takes place in the mitochondria, and photophosphorylation,[329,330] investigated with chloroplasts from the membrane of *Halobacterium halobium.*

4.6.1.2.4. Miscellaneous functions of lipoic acid Lipoic acid is found to intervene in a wide variety of biological processes as summarized in the following: Prostaglandine biosynthesis is influenced by lipoic aid[343-346] as are various enzymes – *i.e.* serine hydroxyl transferase,[347] rhodanese,[348] disulfide reductase,[349,350] 5'-deiodinase[351] and hog liver monooxygenase[352] — the maltose binding protein of *E. coli*,[353] the metabolism of nicotinic acid,[354] certain transport systems of *E. coli*,[355] and the absorption of thiamin in dogs.[356] Finally, lipoic acid is reported to be responsible for the decarboxylation of glycine acting as a coenzyme for the hydrogen carrier protein, a component of the glycine cleavage system.[357,358] The metabolism of lipoic acid seems to be age related at least in the rat.[359]

4.6.1.3. Biosynthesis During the last decade extensive studies on the biosynthetic pathway leading to lipoic acid have been performed;[360-369] however, a complete understanding of the reaction sequences has not been achieved. Isotope labeling experiments have indicated that octanoic acid is a precursor of lipoic acid, and that the sulfur atoms are introduced at C-6 and C-8 by apparent substitution of two hydrogen atoms. This reaction is very unlikely from a chemical point of view, but biological systems seem to

have developed an ability to accomplish such substitutions on saturated carbon. For instance, the introduction of sulfur into biotin and penicillin is conducted in the same manner.[368] Substitution of sulfur at C-6 occurs with inversion of configuration.[362] The sulfur atoms of lipoic acid are believed to originate from cysteine.[368,369]

Investigations of the catabolic reactions of lipoic acid are on record.[370-372]

4.6.1.4. Practical applications An overwhelming number of biological activity tests involving lipoic acid have been reported in the literature. A brief summary of positive results is given in the following.

Lipoic acid and derivatives have been tested for their radiation protective ability;[373-382] the results, however, are ambiguous. One group of authors find only a slight protective effect of lipoic acid on the central nervous system,[373] whereas another group describes an O_2-dependent radio-sensitizing effect of lipoic acid on spores of *Bacillus megaterium*.[374] The most thoroughly investigated lipoic acid derivative in this context is diethyllipoamide.[379-381]

Lipoic acid and derivatives have been applied in cancer therapy.[285,383-389] Work concerning the cytostatic effects of a number of 1,2-dithiolane derivatives showed lipoic acid to be active against fibroblasts from mice, whereas no activity was found against Ehrlich tumor cells.[285] Likewise, no protective effect of lipoic acid on the development of tumors, induced by the carcinogen *N*-nitrosodiethylamine, was detected.[383] Lipoic acid, however, seems to reduce the toxic side effects of certain chemotherapeutics;[385] the use of lipoic acid in the prevention of hair loss caused by cytostatic chemotherapy has been patented.[386]

Various carbohydrate derivatives of lipoic acid have likewise found application in multistep cancer therapy,[388] and the S–S polymer of *N*-lipoyl-β-D-(mannopyranosyl)-amine has been proven to be active in the selective transfer of therapeutics to macrophages.[384]

Besides these therapeutic usages, lipoic acid may exert a cancer protective action by inhibiting the nitrosation of tyrosin under conditions corresponding to those in the stomach.[389]

As a result of the metal complexing properties of lipoic acid and dihydrolipoic acid (Sect. 3.4.4) these compounds have been successfully applied in the treatment of heavy-metal poisoning.[390-395] Lipoic acid derivatives are extremely active towards both mercury[390-392] and cobalt poisoning,[393,394] although lipoic acid does not appear to influence the secretion of organic mercury compounds.[395]

Lipoic acid and its derivatives possess a detoxification effect against a variety of chemicals: CCl_4,[396-400] arsenic compounds,[401-406] allyl alcohol,[407] thioacetamide[407] and 8-quinolinol.[408]The biochemical mode of action of lipoic acid upon arsenite and arsenate is partly known.[401,409] Dihydrolipoic acid is believed to act as a reducting agent in the transformation of these compounds into trimethylarsine. Lipoic acid exhibits no effect on caries, induced by the related tellurium compounds, sodium tellurate[410] and sodium tellurite.[411]

Investigations of the effect of lipoic acid on mushroom alkaloid poisoning have been recorded.[412-414] The results of these investigations are discordant. One group of authors[412] describes lipoic acid as being remedial in the treatment of children poisoned by *Amanita phalloides*, whereas another group[413] does not find any effect of lipoic acid,

administered to mice poisoned by the same mushroom. For a further discussion on this subject cf. ref.[414 and refs. herein]

Lipoic acid has been applied in the treatment of several chronic and acute diseases. An advantageous effect of lipoic acid in diabetes has been reported.[415-417] This effect is believed to be due to stimulation of pyruvate dehydrogenase and to a lowered rate of oxidation of fatty acids and of gluconeogenesis. Likewise a useful effect of lipoic acid on atherosclerosis is described,[418,419] explained by a reduction of the cholesterol content of the serum. Effects of lipoic acid in ischemia,[420] pancreatitis,[421] hepatitis[422,423] and perinatal hypoxia[424] have been reported.

Several records of additional biological activities of lipoic acid are found in the literature — *i.e.* the influence of lipoic acid on: coagulation factors,[425] the glycogen level in the brain during CO poisoning,[426] the responses of various cell cultures to erythrocytes[427-430] and other antigens,[420,429,430] the biological redox processes in animals exposed to formaldehyde,[431] ethanol metabolism,[432] the embryonal development of various marine organisms[433 and refs. herein] and the immune system of mice.[434] Furthermore, a hemolytic effect on humane erythrocytes,[435] antimicrobial activities,[436,437] antimutagenic activities,[438] cytoprotective activities[439] and hepatoprotective activities[440] of lipoic acid have been reported.

4.6.2. Lipoic acid S-*oxide* Lipoic acid *S*-oxide (protogen B, β-lipoic acid) was originally identified as an oxidation product of lipoic acid.[13] It was a long-standing question whether or not lipoic acid *S*-oxide was an artefact arising during isolation and work-up of lipoic acid. The natural occurrence of lipoic acid *S*-oxide in various biological systems was subsequently established,[264 and refs. herein] and it is believed to be a metabolite of lipoic acid,[264,370-372,441] along with bisnorlipoic acid (1,2-dithiolane-3-propanoic acid) and tetranorlipoic acid (1,2-dithiolane-3-carboxylic acid) (Sect. 4.3.1). The structure of lipoic acid *S*-oxide has been established to be 5-(1-oxo-1,2-dithiolan-3-yl)pentanoic acid.[264]

*4.7. 4-(*N,N-*Dimethylamino)-1,2-dithiolane (Nereistoxin)*

4.7.1. Natural occurrence and functions Nereistoxin was isolated in 1938[6] from the marine annelid *Lumbriconereis heteropoda* (a common bait used by Japanese anglers). Its presence was recognized since insects which came in contact with the worm were paralyzed and eventually died. The structure of nereistoxin was elucidated thirty years later.[7,8]

Neither the biosynthesis nor the biological function of nereistoxin have been described. Since *Lumbriconereis* is capable of active transfer of poison, either by bite or from its bristles,[442] it is probable that nereistoxin serves a purpose partly in hunting and partly as defense since nereistoxin is known to be toxic towards fish as well as insects.[7]

4.7.2. Practical applications Several biological experiments illustrating the insecticidal activity of nereistoxin have been reported,[52,443,444] and it has been indicated that certain commonly used insecticides — *e.g.* cartap [1,3-bis(carbamoylthio)-2-*N*,*N*-dimethylaminopropane] — are transformed into nereistoxin in the target organism, and exert their action in this way.[445-449]

The biochemical background for the insecticidal action of nereistoxin has been

thoroughly investigated.[442,450-467] Nereistoxin is a nerve poison, acting on cholinergic synapses (*i.e.* the neurotransmitter is acetylcholine). These synapses are found in brain tissue, ganglia, neuroglandular junctions as well as neuromuscular junctions in vertebrates. The binding of the neurotransmitter to its receptor is believed to result in a conformational change which influences the channels responsible for the flow of inorganic ions.[456,467]

The toxicity of nereistoxin is ascribed to a blockage of cholinergic transmission by a reduction of the amount of transmitter released from the synaptic vesicles in the presynaptic membrane and by lowering the sensitivity of the postsynaptic membrane towards acetylcholine. It remains to be seen whether nereistoxin acts directly on the receptor or on the channels controlling the ion permeability and it is also possible that nereistoxin is active towards more than one site.[461]

*4.8. 5-(*N,N-*Dimethylamino)-1,2,3-trithiane*

Although the title compound is not naturally occurring its inclusion in this work is justified by the fact that 5-(*N,N*-dimethylamino)-1,2,3-trithiane is by far the most thoroughly investigated representative of the 1,2,3-trithianes, because of its commercial use as an insecticide. 5-(*N,N*-Dimethylamino)-1,2,3-trithiane hydrogen oxalate is manufactured under the trade marks Thiocyclam hydrogen oxalate, Sultamine, SAN 155 I and Evisect. This trithiane is characterized as a nereistoxin derivative, and its mode of action is believed to be analogous to that of nereistoxin.[468] 5-(*N,N*-Dimethylamino)-1,2,3-trithiane is a contact and stomach insecticide, shown to be especially active against larvae and grown individuals of the orders *Lepidoptera* and *Coleoptera*, which include important pests of several crops.[469]

For the results and discussions of the biological tests see the original literature.[41,91,470-514]

4.9. 4-(Methylthio)-1,2-dithiolane (Charatoxin) and Its Analogs

4.9.1. Natural occurrence and biological functions Charatoxin was originally isolated from *Chara globularis*,[66] and its presence in other Chara species has subsequently been established.[515] These pungent-smelling green algae are dominating the algae flora in the ecosystem of which they are a part. This dominating effect is due to the presence of some extremely active photosynthesis inhibitors, namely 4-(methylthio)-1,2-dithiolane and 5-(methylthio)-1,2,3-trithiane. The trithiane is by far the most active of the two, although less active than elemental sulfur, which was also found to be present during the isolation of the title compounds.

4.9.2. Practical applications Since charatoxin shows a close structural resemblance to nereistoxin the insecticidal activities of the title compounds have been tested.[516,517] The insects tested were apparently affected in a comparable manner — *i.e.* paralysis and eventually death — although the lethal doses were higher.

The effect of charatoxin on the frog sartorius neuromuscular junction has been investigated,[517] and it was established to be comparable to that of nereistoxin.

Recent work,[466] dealing with the interactions of charatoxin (and open-chain analogs) and nereistoxin with the nicotinic acetylcholine receptors from the central nervous system of honey bees (*Apis mellifera*) and from the electric organ of the electric ray (*Torpedo californica*), establishes that the mechanisms of action of these toxins — on the same target — are different, as are the responses to the toxins of receptors of different origin — *i.e.* insect or vertebrate.

ADDENDUM

During the preparation of this manuscript additional literature, relevant to the present subject, has been published. This material is summarized in the following.

Synthesis

The following results on the synthesis of 1,2-dithiolanes and 1,2,3-trithianes are recorded: Synthesis of asparagusic acid derivatives from penicillin sulfoxides,[528] a new synthesis of (R)-(+)-lipoic acid from L-(-)-di(*i*-propyl) tartrate and (E)-2,8-nonadienol,[529] improved enantiospecifc syntheses of (R)-(+)-lipoic acid from D-glucose[530] and of (R)-(+)- as well as (S)-(−)-lipoic acid from (S)-malic acid[531] and a synthesis of (±)-lipoic acid from methyl 6,8-dihydroxyoctanoate, which was prepared by a highly regioselective allylic oxidation of methyl 7-octenoate, followed by hydroboration-oxidation.[532] Nereistoxin analogs have been prepared in high yield from *N*,*N*-dimethyl-2,3-dichloropropanamine and sodium polysulfide,[533] and the trithiane analog, 5-(*N*,*N*-dimethylamino)-1,2,3-trithiane · HCl, has been synthesized (90%) from the corresponding bis(thiosulfate) and Na_2S.[534] A new synthesis of cyclic polysulfides, including 1,2,3-trithiane, from dithiols or derivatives and elemental sulfur in liquid ammonia is reported.[535]

Physico-Chemical Properties

In an NMR spectroscopic study of the barrier to pyramidal inversion of sulfur in pentacarbonylchromium complexes of sulfides data on 4,4-dimethyl-1,2-dithiolane are reported,[536] as are IR and Raman spectroscopic data on 1,2,3-trithiane.[537]

Chemical Reactions

The oxidation of 5-, 6- and 7-membered cyclic disulfides with various oxidizing agents has been thoroughly investigated, and the reactivities of the resulting 1,1-dioxides towards thiolate ions have been compared.[538] The radical cation of lipoic acid has been prepared by one-electron oxidation of lipoic acid.[539]

Reduction potentials of several sulfur containing radicals, including the radical anion of lipoamide, have been recorded.[540] The reduction of lipoic acid to dihydrolipoic acid is the basis for a potentiometric method, employing a gold electrode coated with a carbohydrate polymer matrix, for the detection of substrates of bacterial metabolism.[541]

Reductive phosphorylation of 1,2-dithiolanes with dialkyl phosphites to yield mono-*S*-phosphorylated 1,3-dithiols has been described.[542] The reductive phosphorylation of

lipoamide in the presence of various carboxylic acid anhydrides results in regioselective formation of 6-*S*-acyldihydrolipoamide derivatives, bearing the dimethyl phosphoryl group on the 8-S atom.

An example of nucleophilic cleavage of the S-S bond in 1,2-dithiolanes is found in the reaction of 4,4-diethyl-1,2-dithiolane with Grignard reagents.[543] These reactions are reported to give high yields of mono-*S*-alkylated 1,3-dithiols.

An example of radical cleavage of the S-S bond in 1,2-dithiolanes is found in the copolymerization of lipoamide and styrene. Thermal copolymerization is initiated by styrene radicals, whereas photoinduced copolymerization is initiated by dithiyl radicals.[544]

The chemistry of polymer-bound lipoic acid and other sulfur-containing polymers has been reviewed.[545]

Biological Properties

The following recent reports of the biological properties and practical applications of 1,2-dithiolanes and 1,2,3-trithianes are found in the literature: The presence of lipoic acid in archaebacteria has been established.[546] Lipoic acid is reported to stimulate prostaglandin formation,[547] to exhibit a cytoprotective effect on gastric mucosa exposed to ethanol[548] and to exert a protective effect on motor nerve terminals in acrylamide poisoned rats.[549] Only a minor effect of lipoic acid on the restoration of sciatic nerves in rats is observed.[550] The influence of lipoic acid on the transport of biotin of humane intestine has been investigated[551,552] and the relation of lipoic acid to early embryonal development, investigated on cultured rabbit morulae, has been described.[553] Furthermore, lipoic acid has been applied in the treatment of skin diseases[554] and is a component of several skin lotions.[555-557] Lipoic acid and derivatives are constituents of hair preparations, used for dandruff control and stimulation of hair growth.[558] The stability of lipoic acid in various pharmaceuticals has been investigated.[559] Finally, the permeability of biological membranes has been studied on liposomes, prepared from phospholipids, derived from lipoic acid.[560]

The influence of 3,3-dimethyl-1,2-dithiolane[561] and 3-propyl-1,2-dithiolane[561,562] and other predator odors on the behavior of certain herbivores has been examined.

A report on multi-component insecticidals, containing 5-(*N*,*N*-dimethylamino)-1,2,3-trithiane, has appeared.[563]

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