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DIVINYL DISULFIDES: SYNTHESIS AND PROPERTIES

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Data on the synthesis, reactivity, physico-chemical properties, and biological activity of divinyl disulfides and of related derivatives of thiamine (vitamin B_1) have been collected and are briefly discussed.

Key words: acetylenes, alkenes, divinyl disulfides, enethiols, sulfur chlorides, thiamine disulfides

CONTENTS

1. INTRODUCTION

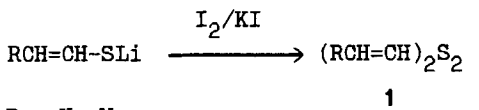
Not withstanding considerable interest during the past decade for divinyl sulfide and its derivatives[1-8] divinyl disulfide and related compounds have been much less emphasized

in the literature. However, as this somewhat summary, but nevertheless exhaustive survey of divinyl disulfide chemistry shows, a considerable amount of relevant work can, in fact, be found. Actually, the divinyl disulfide structural unit occurs not infrequently in organic sulfur chemistry as well as in biochemistry, playing a distinct role in a number of electron transfer processes. Divinyl disulfides are in many cases stable redox derivatives of highly reactive enethiols and thiones and thus of particular interest also in this context.

2. SYNTHESIS OF DIVINYL DISULFIDES

2.1. Oxidation of Enethiols

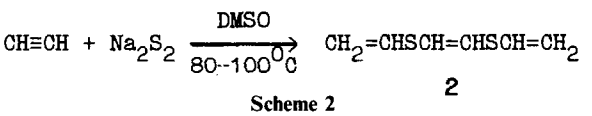
Symmetrical di(1-alkenyl) disulfides **1** can be conveniently prepared from the alkenethiolate solutions produced by cleavage of alkyl vinyl sulfides with lithium metal in liquid ammonia. For this purpose the ammonia is removed by evaporation, then water is added and the resulting aqueous alkenethiolate solution oxidized with iodine.[9]



Scheme 1

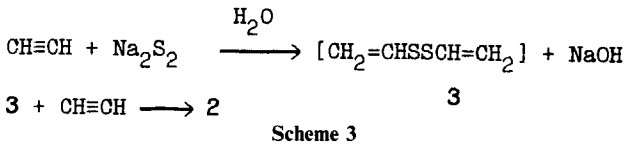
Satisfactory syntheses of 1-alkenyl alkyl disulfides, RS–S–CH=CHR′, and di(1-alkenyl) disulfides, $(R'CH{=}CH)_2S_2$, have been developed by Wijers *et al.*[9,163]

When the reaction of acetylene with sodium disulfide was carried out in wet DMSO none of the expected divinyl disulfide was obtained. Together with divinyl sulfide, 1,2-bis(vinylthio)ethene **2** was isolated in about 10% yield.[10,11]



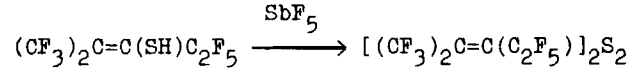
Scheme 2

Compound **2** seems to be formed from the intermediate divinyl disulfide **3** by addition to acetylene. Reactions of this kind are typical of organic disulfides.[12]



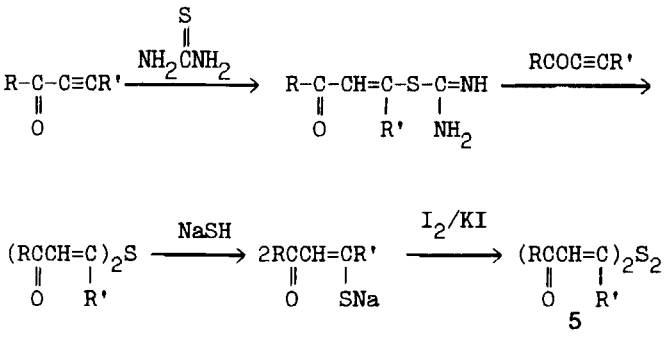
Scheme 3

When treated with SbF_5, perfluorinated enethiols are oxidized to the corresponding disulfides **4**.[13]



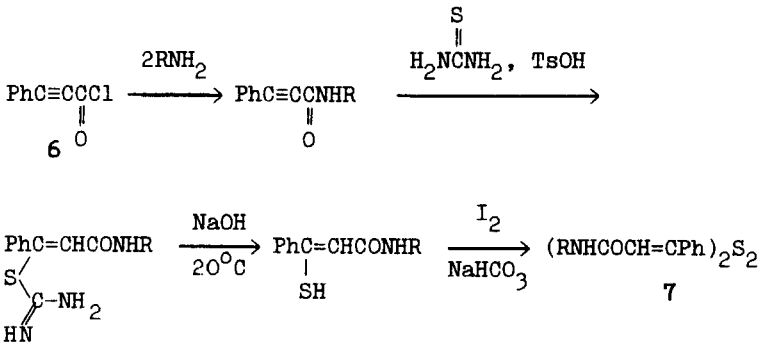
Scheme 4

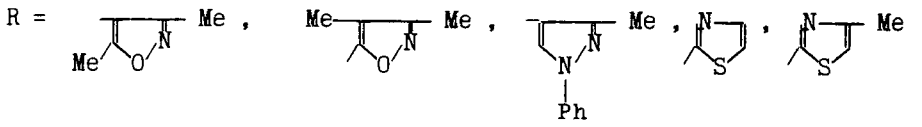
Bis(acylvinyl) sulfides, obtained by reaction of α-acetylenic ketones with thiourea in alcohol at room temperature in the presence of a basic catalyst or by treatment of the appropriate ketones with sodium hydrosulfide and oxidation of the thiol thus generated with an I_2/KI system, have been converted to the corresponding disulfides **5**.[14]



Scheme 5

From phenylpropiolic acid chloride **6** the disulfides **7** with different heterocyclic substituents in the amide moiety have been prepared according to the following scheme:[15]





Scheme 6

The enethiols **8** have been oxidized with air oxygen to the disulfides **9**.[16]

$$\underset{\mathbf{8}}{PhNH{=}C(SH)CONHR} \xrightarrow{air} \underset{\mathbf{9}}{[PhCH{=}C(CONHR)]_2S_2}$$

R = Me, Et, Pr, i-Pr, n-Bu

Scheme 7

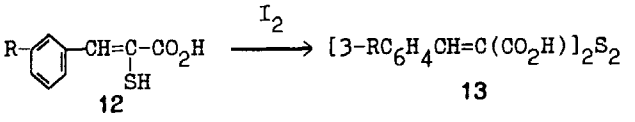
Treatment of 1,1-dicyano-2-amino-2-(methylthio)ethene **10** with sodium hydrosulfide, followed by oxidation of the enethiol with 30% H_2O_2, gave the disulfide **11** in 90% yield.[17-19]

By means of this reaction thirty-seven divinyl disulfides with different substituents (CN, CO_2Et, CONHMe, etc.) have been prepared.[20]

$$\underset{\mathbf{10}}{(NH_2)C(SMe){=}C(CN)_2} \xrightarrow{NaSH} (H_2N)C(SH){=}C(CN)_2 \xrightarrow{30\%\ H_2O_2} \underset{\mathbf{11}}{[(NC)_2C{=}C(NH_2)]_2S_2}$$

Scheme 8

Iodine oxidation (with iodine dissolved in aqueous KI) is the most widely accepted technique.[21-23] However, treatment of the β-aryl-α-mercaptoacrylic acids **12** with excess iodine in 1,2-dimethoxyethane leads to the sulfides **13** rather than to the expected disulfides.[24]

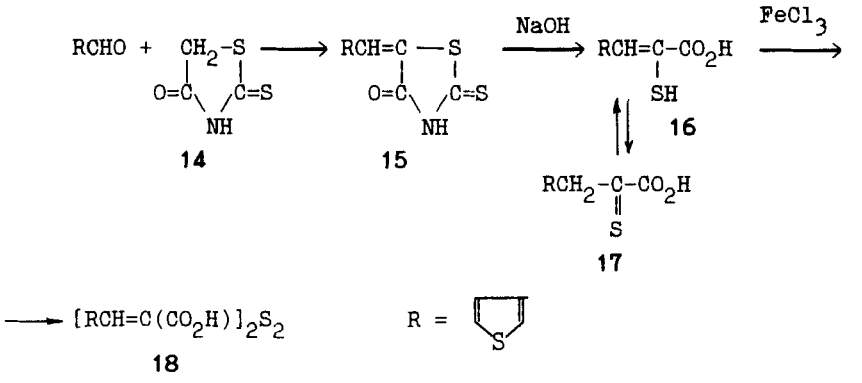


12 **13**

R = F, Cl, Br

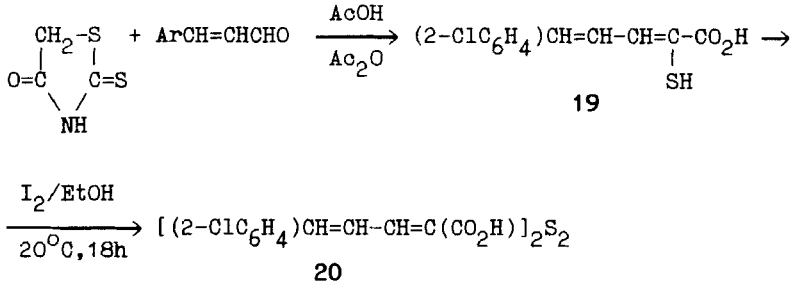
Scheme 9

The condensation of aldehydes with rhodanine (1,3-thiazolidin-4-one-2-thione) **14**, followed by alkaline cleavage of the products **15**, is one of the methods for preparation of the α-mercaptoacrylic acids **16** and the corresponding divinyl disulfides **18**.[25,26] The alkylidenerhodanines **15**, prepared in high yields, were cleaved with sodium hydroxide to give the acids **16** in equilibrium with their thiono isomers **17**. The oxidation of **16** with iron(III) chloride leads to the disulfides **18**.



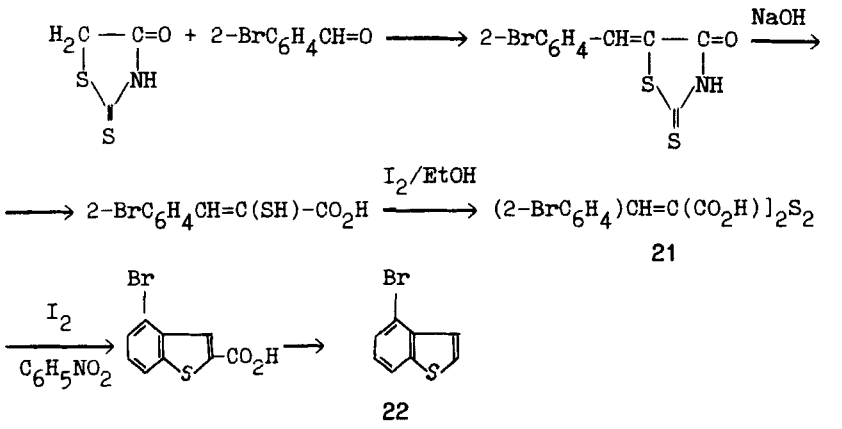
Scheme 10

Likewise, 2,2-dithiobis-5-(2-chlorophenyl)-2,4-pentadienoic acid **20** has been prepared.[27] The intermediate 2-mercapto-5-(2-chlorophenyl)-2,4-pentadienoic acid **19** was oxidized with iodine in EtOH at room temperature over 18 h.



Scheme 11

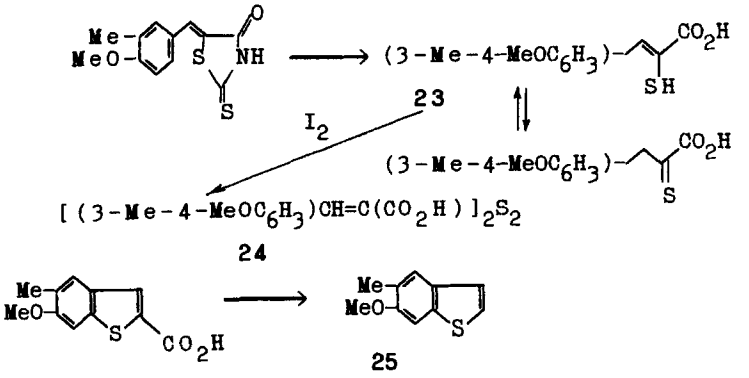
Analogously, from rhodanine the disulfide **21** has been prepared.[28]



Scheme 12

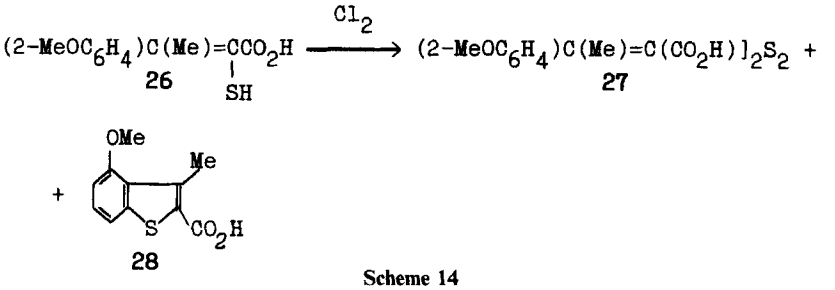
Under certain conditions this reaction can be directed towards the formation of benzothiophene **22**.

Formation of the benzothiophene derivatives **25**,[29,30] together with the disulfide **24**, was observed in the oxidation by iodine of β-(3-methyl-4-methoxyphenyl)-α-mercaptoacrylic acid **23**, also prepared from rhodanine.



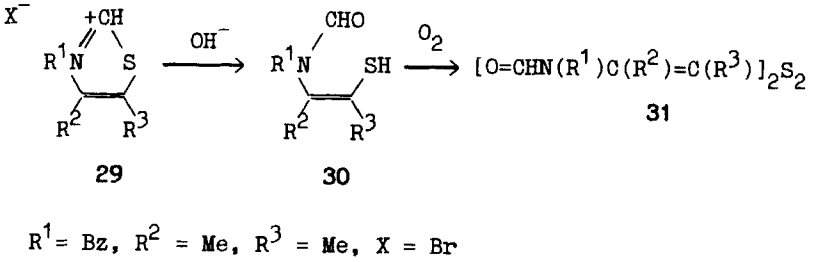
Scheme 13

As reported in,[31] the oxidation by chlorine of α-mercaproacrylic acid **26** gives the disulfide **27** together with the expected benzothiophene **28**.



Scheme 14

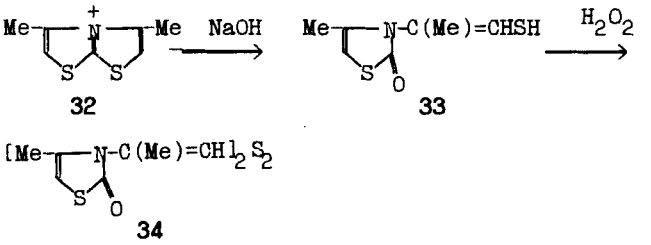
For the preparation of the enethiols **30** and divinyl disulfides **31** use was made of the thiazolium salts **29**.[32]



R^1 = Bz, R^2 = Me, R^3 = Me, X = Br

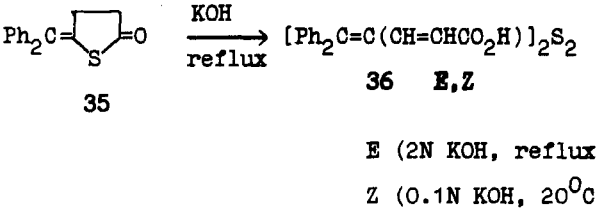
Scheme 15

Under the action of sodium hydroxide ring opening of the thiazolo[2,3-*b*]thiazole system **32** occurs and after oxidation (H_2O_2) of the ensuing enethiol **33** the disulfide **34** is obtained.[33]



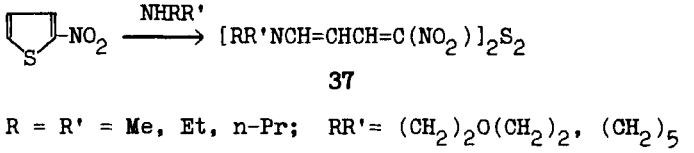
Scheme 16

As a result of the hydrolysis of 5-(diphenylmethylene)-2(5*H*)-thiophen-2-one **35**, the divinyl sulfide **36** is formed.[34] Its *E*- and *Z*- forms can be prepared mainly by use of KOH in different concentrations.



Scheme 17

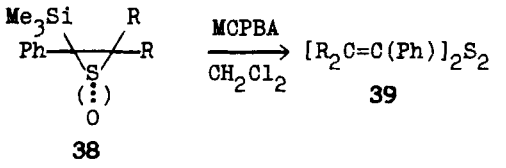
For the preparation of substituted bis-1,3-butadienyl disulfides **37** use was made of the reaction of 2-nitrothiophene[35,36] with amines in EtOH.



Scheme 18

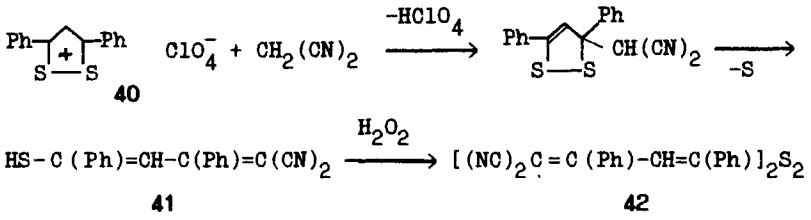
The structure of the disulfide **37** has been examined by X-ray diffraction.[35]

The oxidation of the organosilicon substituted thiiranes **38** with *m*-chloroperbenzoic acid (MCPBA) leads to the divinyl disulfides **39**.[37]



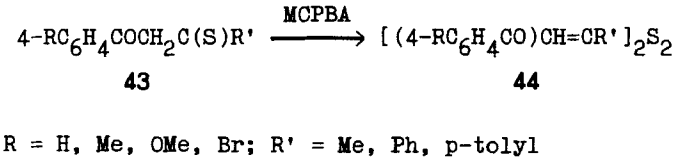
Scheme 19

The reaction of 3,5-diphenyl-1,2-dithiolium perchlorate **40** with malonitrile yields 1,3-diphenyl-4,4-dicyano-1,3-butadiene-1-thiol **41**, oxidation of which leads to the divinyl disulfide **42**.[38]



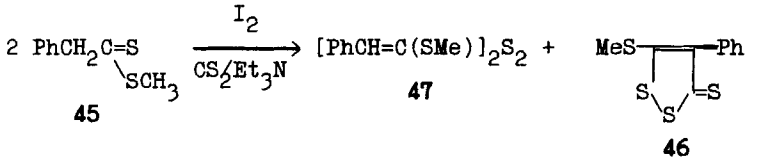
Scheme 20

In a number of cases, divinyl disulfides are also formed by oxidation of different thiono compounds which are tautomers of enethiols. However, it remains uncertain whether a preliminary isomerization to enethiols takes place or if the thiono compounds are directly oxidized to disulfides. Thus, the 2-thioacylacetophenones **43** have been oxidized with MCPBA to the divinyl disulfides **44**.[39]



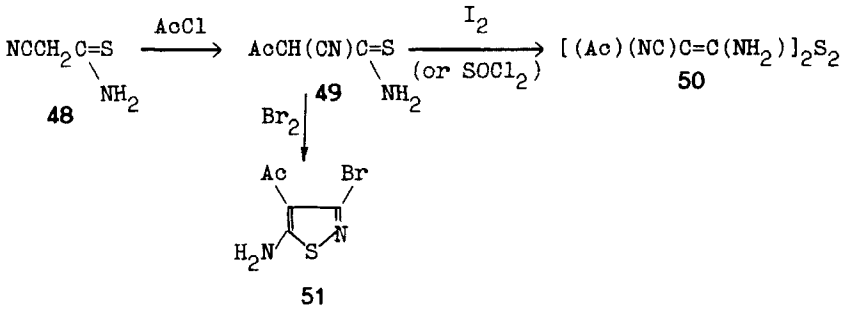
Scheme 21

In a study of the oxidation of dithioester **45** in the CS_2/Et_3N system, the divinyl disulfide **47** was obtained together with the cycloadduct **46**.[40] The yield of the disulfide depends on the strength of the oxidant: in the presence of sulfur only traces of disulfide are formed, whereas iodine oxidation leads to quantitative yields of **46**.



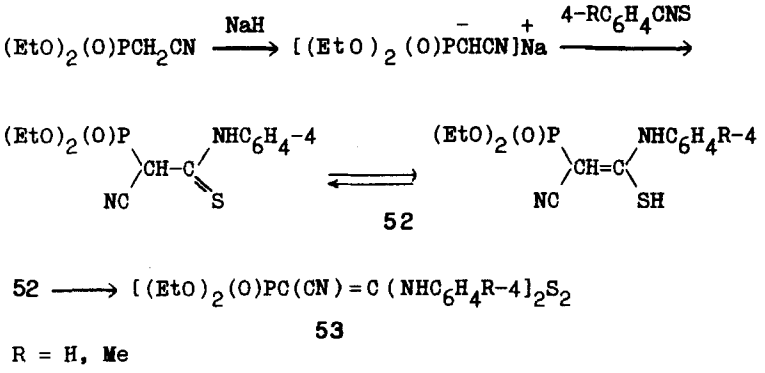
Scheme 22

Cyanothioacetamide **48** reacts with acetyl chloride in pyridine to give α-cyano-α-acetylacetamide **49**, which, when oxidized with iodine or thionyl chloride, gives the disulfide **50**.[41] Bromine oxidation of **49** affords the isothiazole **51**.



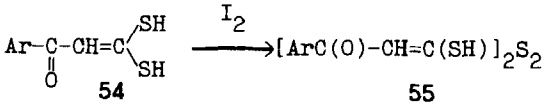
Scheme 23

In its reaction with bromine the α-cyanosubstituted thioamide **52** does not undergo the expected cyclization. Instead, it forms the disulfide **53**. The same was observed upon oxidation with ethanolic iodine solution.[42]



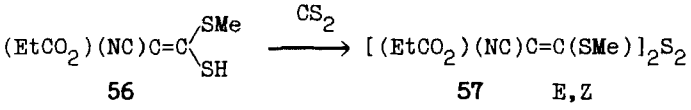
Scheme 24

Enedithiols and their derivatives are also readily oxidized to the corresponding divinyl disulfides. Thus, the 3,3-dimercapto-1-aryl-2-propen-1-ones **54** have been oxidized with iodine solution (or with air oxygen) to the disulfides **55**.[43]



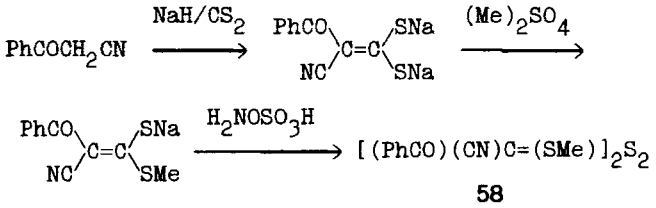
Scheme 25

Refluxing ethyl 2-cyano-3-mercapto-3-(methylthio)-acrylate **56** in CS_2 leads to a mixture of the *E*- and *Z*-forms of disulfide **57**.[44]



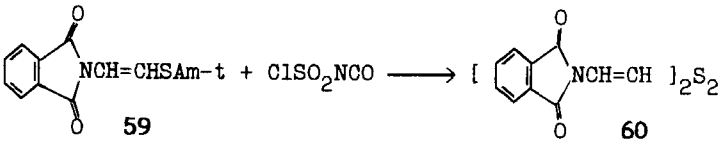
Scheme 26

Upon dithiocarboxylation of benzoylacetonitrile the divinyl disulfides **58** were obtained.[45]



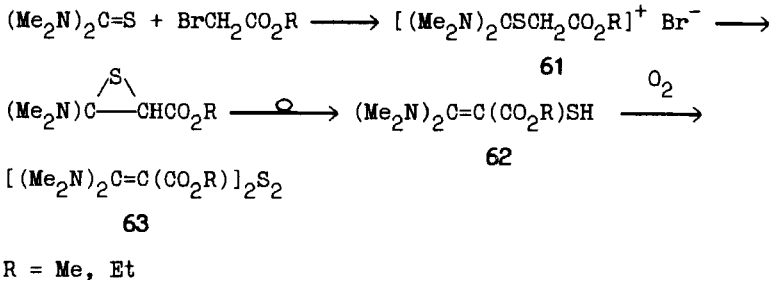
Scheme 27

Examples of oxidative transformation of certain vinyl sulfides to divinyl disulfides are known. Thus, disulfide **60** has been obtained in about 50% yield by treatment of the vinyl sulfide **59** with chlorosulfonyl isocyanate.[46]



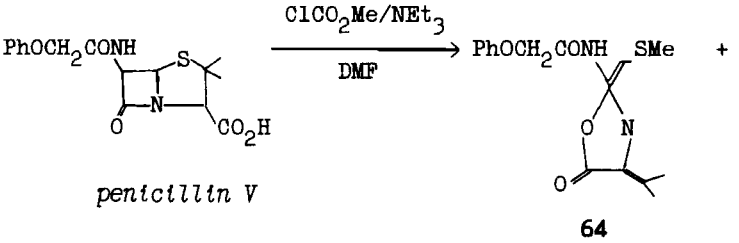
Scheme 28

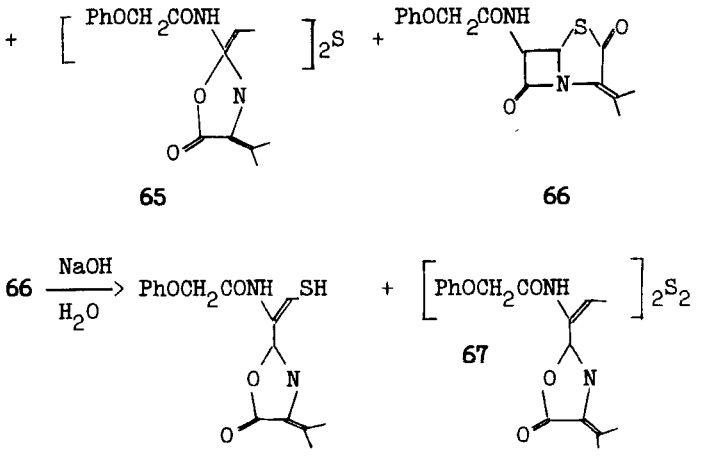
In,[47] the enethiols **62**, obtained from the salts **61**, were oxidized to the disulfides **63**.



Scheme 29

Divinyl sulfides which are penicillin derivatives are known.[48] Treatment of penicillin V with triethylamine and methyl chloroformate in DMF gives the divinyl sulfide **65**, together with the products **64** and **66**.

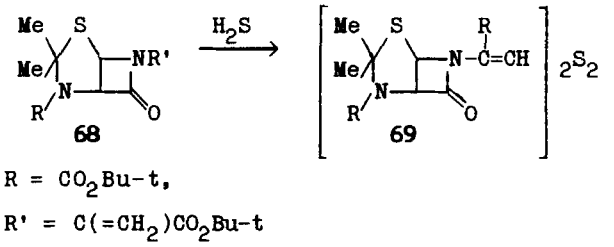




Scheme 30

Alkaline hydrolysis of **66** leads to the divinyl disulfide **67**.

Treatment of the β-lactam **68** with hydrogen sulfide and removal of the protective group with CF_3CO_2H afforded the divinyl disulfide **69**.[49]



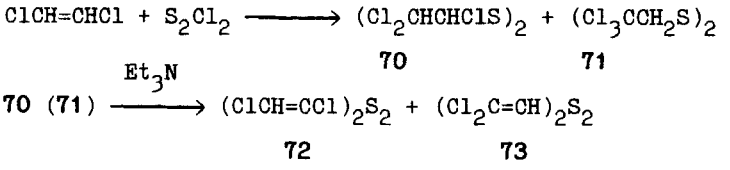
R = CO_2Bu-t,

R' = $C(=CH_2)CO_2Bu$-t

Scheme 31

2.2. *Addition of Sulfur Chlorides to Alkenes and Acetylenes*

Addition of S_2Cl_2 to 1,2-dichloroethylene gave the disulfides **70** and **71** which were further converted to the divinyl disulfides **72** and **73** by dehydrochlorination (Et_3N).[50]



Scheme 32

By addition of SCl_2 to methyl 1-(acetylamino)acrylate **74** and subsequent elimination of hydrogen chloride the divinyl disulfide **75** has been obtained.[51]

$$\underset{\mathbf{74}}{(AcNH)(MeCO_2)C{=}CH_2} \xrightarrow[-HCl]{SCl_2} \underset{\mathbf{75}}{[(AcNH)(MeCO_2)C{=}CH]_2S_2}$$

Scheme 33

The divinyl disulfides **76** have been prepared from alkenes and S_2Cl_2 according to the following scheme:[52]

$$R^2R^3NCH{=}CHR^1 \xrightarrow[20^0C]{S_2Cl_2} \underset{\mathbf{76}}{(R^2R^3NCCl{=}CR^1)_2S_2}$$

R^1 = Me, Ph; R^2 and R^3 = Me or Et

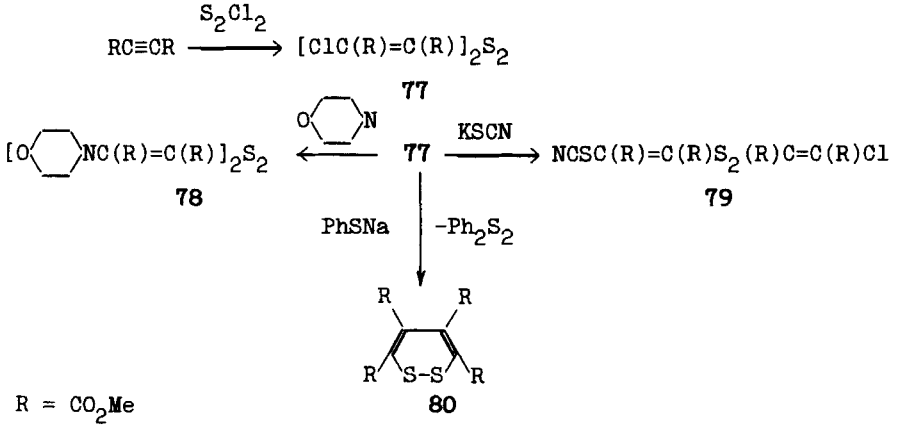
Scheme 34

Unlike the disulfide $CF_3CH(CH_2Cl)S_2CH_2Ph$, which is prone to facile dehydrochlorination, the symmetrical disulfide cannot be dehydrochlorinated neither with the weak base *N*-methylpyrrolidone nor with Et_3N.[53] In the latter case a mixture of unidentified resinous products is formed.

$$[CF_3CH(CH_2Cl)]_2S_2 \xrightarrow{\times} [CH_2{=}C(CF_3)]_2S_2$$

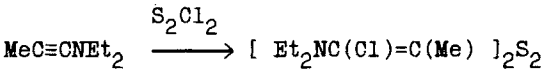
Scheme 35

The reaction of dimethyl acetylenedicarboxylate with sulfur chloride leads to the disulfide **77** (70% yield) which reacts with morpholine at 0 °C to form the disulfide **78** (50% yield) or with KSCN to form the disulfide **79** (60% yield), whereas with PhSNa tetramethyl-1,2-dithiin-3,4,5,6-tetracarboxylate **80** is formed (60% yield).[54,55]



Scheme 36

The reaction of S_2Cl_2 with 1-(*N*,*N*-diethylamino)propyne gives a mixture of the *E*,*Z*-, *E*,*E*- and *Z*,*Z*-isomers of the disulfide **81**.[56]

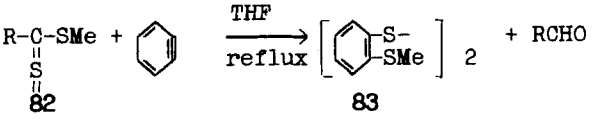


81

Scheme 37

2.3. *Other Methods*

Reaction of the dithioesters **82** with benzyne affords the disulfides **83** along with aldehydes.[57]

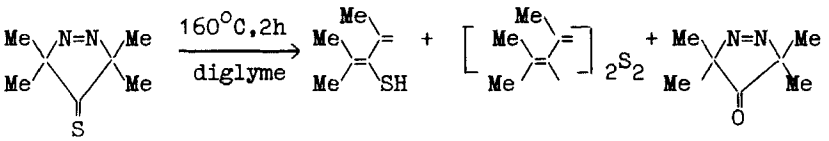


82 **83**

R = t-Bu, Ph, Me(Ph)C=CH-

Scheme 38

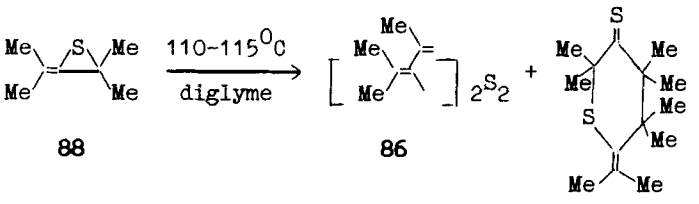
Thermolysis of pyrazoline-4-thione **84** with carbonyl compounds such as *p*-nitrobenzaldehyde in diglyme (160 °C, 2 h) gives the divinyl disulfide **86** in a yield of up to 21% along with the products **85** and **87**.[58]



84 **85** **86** **87**

Scheme 39

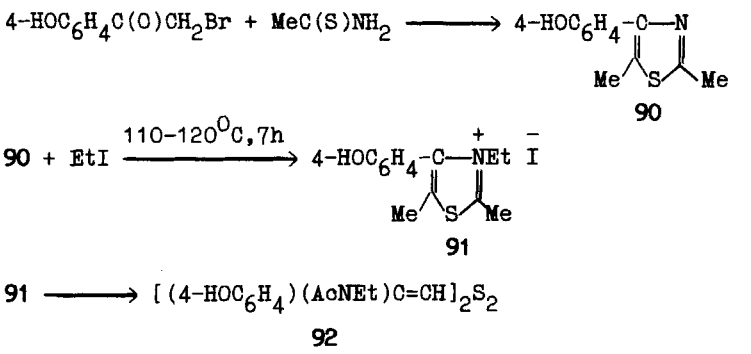
Thermolysis of tetramethylallene episulfide **88** with carbonyl compounds in diglyme (110–115 °C) affords the divinyl disulfide **86** and its dimer **89** in less than 10% total yield.[59]



88 **86** **89**

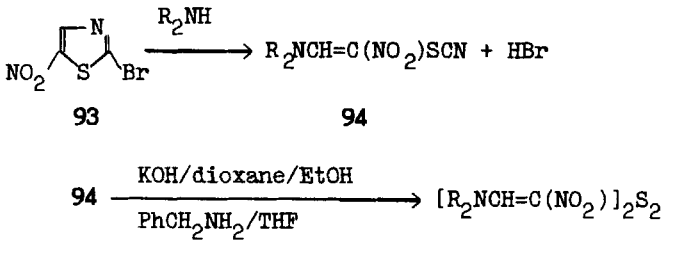
Scheme 40

From the thiazolium salts **91** it is possible to obtain the divinyl disulfide **92** by the following reactions:[60]



Scheme 41

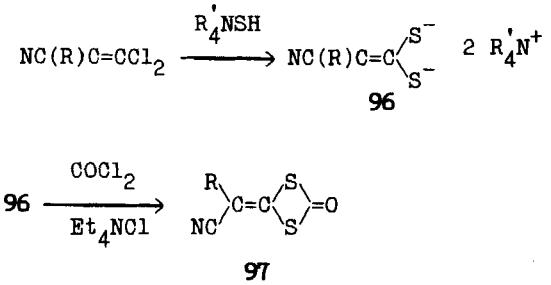
The reaction between the 2-halonitrothiazole **93** and sterically hindered amines in DMSO follows the scheme:[61]

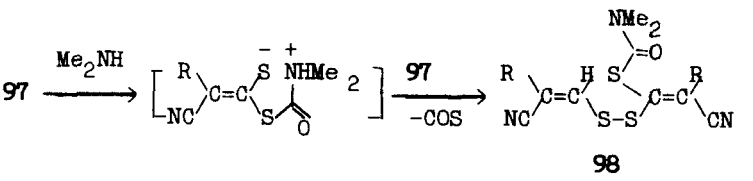


Scheme 42

Under the action of potassium hydroxide in an alcohol-dioxan solution at room temperature, 1-nitro-2-(*N*,*N*-dicyclohexylamino)-vinyl thiocyanate **94** gives the disulfide **95**. The reaction with benzylamine in tetrahydrofuran proceeds in a similar manner.

The unsymmetrical divinyl disulfides **98** have been obtained from 1,1-dichloro-2-cyanoalkenes according to the following scheme:[62]



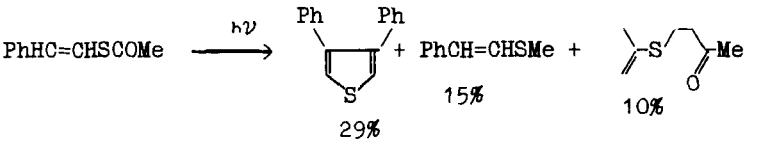


R = Me, t-Bu

R' = Me, Et, Pr, Bz, $Me_2C_6H_3$

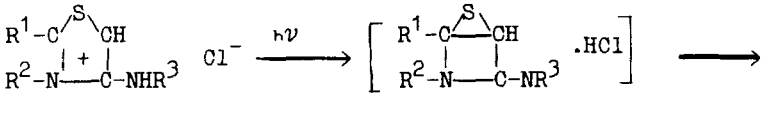
Scheme 43

Styryl thioacetate, when irradiated, gives predominantly 3,4-diphenylthiophene, whereas *S*-β-t-butylvinyl thioacetate under the same conditions forms bis(β-t-butylvinyl) disulfide **99**.[63]



Scheme 44

Formation of the divinyl disulfides **100** in 12–23% yield is observed when mesoionic 1,3-thiazolidines are exposed to irradiation for 6 h.[64]



$[PhNHC(R)=C(CN)]_2S_2$ + $PhC(O)CH_2C(NH)NHPh$ + H_2S

100

R = Ph , Me

$R^1 = R^2$ = Ph, R^3 = H

R^1 = Ph, R^2 = Ph, R^3 = H

$R^1 = R^2$ = Ph, R^3 = COMe

Scheme 45

Metal carbonyls react with sulfenyl chlorides in polar solvents to afford disulfides, including unsaturated ones.[65]

$$RSCl + M(CO)_n \longrightarrow R_2S_2$$

M = Cr, Fe, Ni; n = 6, 5, 4, resp.

R = alkyl, aryl, perhaloalkyl

Scheme 46

This method is generally applicable and proceeds under particularly mild conditions (< 0 °C) to give high yields (> 90%) of disulfides. In the case of perchloro- or perbromoalkanesulfenyl chlorides, the formation of the S–S linkage is followed by an additional partial dehalogenation of the alkyl groups.

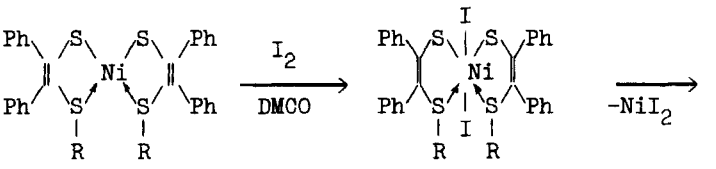
$$Cl_3CCCl_2SCl + Fe(CO)_5 \xrightarrow{THF} (CCl_2{=}CCl)_2S_2$$

101

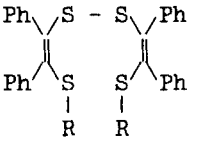
Scheme 47

The disulfide **101** reacts with $Fe(CO)_5$ or $Ni(CO)_4$ to give the polymeric complexes $[Fe(CO)_2(SCCl{=}CCl_2)_2]_n$ and $[Ni(CO)_4(SCCl{=}CCl_2)_2]_n$.

Upon iodination of Ni-, Pd-, and Pt-complexes of the type **102** the divinyl disulfides **103** have been isolated.[66]



102



103

R = Et, Bu

Scheme 48

The divinyl tri- and tetrasulfides **104** have been obtained[67] from thiols and $S_{n-2}Cl_2$.

$$2RSH + S_{n-2}Cl_2 \longrightarrow R\text{-}S_n\text{-}R + 2HCl$$

104

n = 3, 4; R = PrC=CHEt, Ph

n = 3–7; R = $PhC{=}CPh_2$, $HO_2CC{=}CHPh$, $HO_2CC{=}CHCH{=}CHPh$, $HO_2CC{=}CHR'$ (R'= 2-furyl)

Scheme 49

Table 1. Symmetrical divinyl disulfides

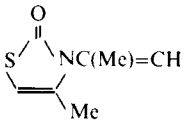
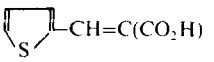
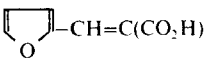
Formula	R	Yield, %	Ref.
$C_4H_6S_2$	CH_2=CH	50–70	9, 163
$C_4H_2Cl_4S_2$	CHCl=CCl	86	50
$C_4H_2Cl_4S_2$	CCl_2=CH	83	50
$C_4Cl_6S_2$	CCl_2=CCl	>90	65
$C_6H_{10}S_2$	MeCH=CH (*Z,Z*)	70	9
$C_6H_{10}S_2$	CH_2=C(Me)		90
$C_6H_8N_2O_2S_2$	$H_2NC(O)CH$=CH (*Z,Z*)	62	87
$C_6H_6Br_2N_2O_2S_2$	$H_2NC(O)CBr$=CH (*E,E*)	78	87
$C_6H_4F_6S_2$	CH_2=C(CF_3)		53
$C_6H_6O_2S_2$	HC(O)CH=CH		14
$C_8H_{12}Cl_2S_2$	MeCHClCH=CH		89
$C_8H_6O_8S_2$	HCO_2CH=C(CO_2H) (*E,E*)		88
$C_8H_4N_6S_2$	$(NC)_2C$=C(NH_2)	92	18, 19
$C_8H_8N_6O_2S_2$	$H_2NCOC(CN)$=C(NH_2)		18, 19
$C_{10}H_8N_6S_2$	$(NC)_2C$=C(NHMe)		18, 19
$C_{10}H_{18}S_2$	Me_2C=CMe		121
$C_{10}H_{18}S_4$	Me_2C=C(SMe)		23
$C_{10}H_{14}O_2S_2$	MeC(O)CH=CMe		122
$C_{10}H_{16}N_2O_2S_2$	EtNHC(O)CH=CH (*Z,Z*)	56	87
$C_{10}H_{12}N_6O_2S_2$	$H_2NC(O)C(CN)$=C(NHMe)		18, 19
$C_{10}H_{10}N_4O_2S_2$	MeC(O)C(CN)=C(NH_2)	54	41
$C_{10}H_{14}O_4S_2$	MeC(OH)=C(COMe) (*E,E*)		68
$C_{12}H_{18}S_2$	MeCH=C(MeC=CH_2)	99	58, 59
$C_{12}H_{22}S_2$	Me_3CCH=CH (*E,E*)	70	63
$C_{12}H_{22}S_2$	Me_3CCH=CH (*E,Z*)	70	63
$C_{12}F_{22}S_2$	$(CF_3)_2C$=C(CF_3)	37	13
$C_{12}H_{12}Cl_2O_6S_2$	$MeCO_2CCl$=CCO_2Me	70	54, 55
$C_{12}H_{18}N_4O_4S_2$	Me_2NCH=CHCH=C(NO_2) (*Z,Z,E,E*)		35, 123
$C_{12}H_{16}N_2O_6S_2$	MeOC(O)C(HNCOMe)=CH	63	51
$C_{12}H_{14}N_4O_4S_2$	$EtCO_2C(CN)$=C(NH_2)	93	18, 19
$C_{12}H_{12}N_6S_2$	$(NC)_2C$=C(NHEt)		18, 19
$C_{12}H_{12}N_6O_2S_2$	MeNHC(O)C(CN)=C(NMe_2)		18, 19
$C_{12}H_{16}N_6O_2S_2$	MeNHC(O)C(CN)=C(NHMe)		18, 19
$C_{12}H_{16}N_6O_2S_2$	$H_2NC(O)C(CN)$=C(NMe_2)		18, 19
$C_{12}H_{12}N_6S_2$	(CN)C=C(NMe_2)		18, 19
$C_{14}H_{16}N_2O_4S_4$	EtOC(O)C(CN)=C(SMe) (*E,E*)	17	44
$C_{14}H_{18}N_4O_4S_2$	EtOC(O)C(CN)=C(SMe)		18, 19
$C_{14}H_{16}N_2O_2S_4$		28	33
$C_{14}H_{10}O_4S_4$			85
$C_{14}H_{10}O_6S_2$			124, 125
$C_{14}H_{26}N_2Cl_2S_2$	$Et_2NC(Cl)$=CMe	62	52
$C_{16}H_{22}N_4O_4S_2$	EtOC(O)C(CN)=C(NMe_2)		18, 19

Table 1. (continued)

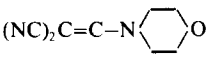
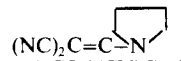
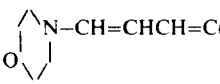
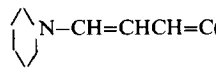
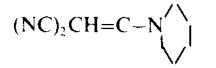
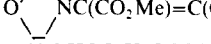
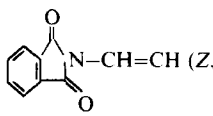
Formula	R	Yield, %	Ref.
$C_{16}H_{16}N_6O_2S_2$			18, 19
$C_{16}H_{16}N_6S_2$			18, 19
$C_{16}H_{22}N_4O_4S_2$	$(MeCO_2)(CN)C=C(NHPr\text{-}i)$		18, 19
$C_{16}H_{22}N_4O_4S_2$			35, 123
$C_{16}H_{26}N_4O_4S_2$	$Et_2NHC=CHCH=C(NO_2)$		35, 123
$C_{16}H_{14}S_2$	PhCH=CH (*Z,Z*)		63
$C_{16}H_{30}N_4O_4S_2$	$(Me_2N)C[N(Me_2)]=C(CO_2Me)$	83	47, 48
$C_{16}H_{30}S_2$	$Me_2C=C(SBu\text{-}t)$		126
$C_{16}H_{30}S_2$	$Me_3CCH_2C(Me)=CH$		127
$C_{18}H_{12}F_2O_4S_2$	$3\text{-}FC_6H_4CH=C(CO_2H)$		24
$C_{18}H_{12}Cl_2O_2S_2$	ClC(O)CH=C(Ph)		15, 128
$C_{18}H_{34}N_4O_4S_2$	$Me_2NC(NMe_2)=C(CO_2Et)$	42	47, 48
$C_{18}H_{14}O_2S_4$	PhC(O)CH=C(SH)		43
$C_{18}H_{12}Br_2S_2$	$2\text{-}BrC_6H_4CH=C(CO_2H)$	100	28
$C_{18}H_{12}Cl_2O_4S_2$	$2\text{-}ClC_6H_4CH=C(CO_2H)$	61	76
$C_{18}H_{12}Cl_2O_2S_4$	$3\text{-}ClC_6H_4C(O)CH=C(SH)$		43
$C_{18}H_{10}Cl_4O_2S_4$	$4,5\text{-}Cl_2C_6H_3C(O)CH=C(SH)$		43
$C_{18}H_{14}O_2S_4$	PhC(O)CH=C(SH)		43
$C_{18}H_{18}S_4$	PhCH=C(SMe)	81	23
$C_{18}H_{26}N_4O_4S_2$	 (*Z,Z,E,*E)		35, 123
$C_{18}H_{20}N_6S_2$			18, 19
$C_{18}H_{12}N_2S_2$	PhC(CN)=CH		129
$C_{18}H_{30}O_6S_4$	$EtOC(O)(CH_2)_3S(O)CH_2CH=CH$		83
$C_{20}H_{18}O_2S_2$	MeC(O)CH=C(Ph)		122
$C_{20}H_{20}N_2O_2S_2$	PhCH=C[C(O)NHMe]	14	16
$C_{20}H_{18}O_4S_2$	PhC(OH)=C[C(OH)=CH_2]		72
$C_{20}H_{28}N_2O_{10}S_2$		50	55
$C_{20}H_{16}Cl_2O_6S_2$	$4\text{-}Cl\text{-}5\text{-}HOC_6H_3C(Me)=C(CO_2H)$		30
$C_{20}H_{18}O_2S_6$	$4\text{-}MeSC_6H_4C(O)CH=C(SH)$		43
$C_{20}H_{34}N_4O_4S_2$	$Pr_2NCH=CHCH=C(NO_2)$ (*Z,Z,E,E*)		35, 123
$C_{20}H_{16}N_2S_2$	PhC(CN)=C(Me)	65	130
$C_{20}H_{18}N_4S_2$	PhNHC(Me)=C(CN)	12	36
$C_{20}H_{12}N_2O_4S_2$	 (*Z,Z*)		46
$C_{22}H_{24}N_2O_2S_2$	PhC(O)N(Me)C(Me)=CH	85	21
$C_{22}N_{24}N_2O_2S_2$	PhCH=C[C(O)NHEt]	41	16
$C_{22}H_{22}O_4S_2$	$4\text{-}MeOC_6H_4C(O)CH=C(Me)$	79	39

Table 1. (continued)

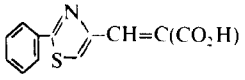
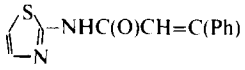
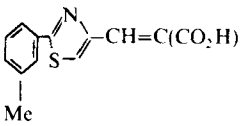
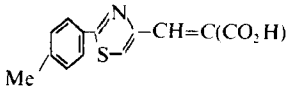
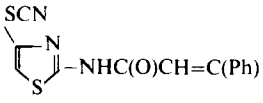
Formula	R	Yield, %	Ref.
$C_{22}H_{22}O_2S_2$	4-$MeC_6H_4C(O)CH=C(Me)$	77	39
$C_{22}H_{16}Cl_2O_4S_2$	2-$ClC_6H_4CH=CHCH=C(CO_2H)$		27
$C_{22}H_{22}O_6S_2$	2-$MeOC_6H_4C(Me)=C(CO_2H)$	72	31
$C_{22}H_{22}O_6S_2$	4-MeO-5-$MeC_6H_3CH=C(CO_2H)$	66	29
$C_{22}H_{22}O_6S_2$	4-Me-5-$MeOC_6H_3CH=C(CO_2H)$	99	29
$C_{22}H_{22}O_6S_2$	4-$MeOC_6H_4CH=C(CO_2Me)$	70	131
$C_{22}H_{22}O_6S_4$	2-MeO-4-$MeOC_6H_3CH=C(SH)$		43
$C_{22}H_{22}O_2S_6$	4-$EtSC_6H_4C(O)CH=C(SH)$		43
$C_{22}H_{16}N_2O_2S_4$	$PhC(O)C(NC)=C(SMe)$	63	45
$C_{24}H_{28}N_2O_2S_2$	$Ph(CH_2)_2N(CHO)C(Me)=CH$		64
$C_{24}H_{28}N_2O_2S_2$	PhCH=C[C(O)NHPr]	28	16
$C_{24}H_{28}N_2O_2S_2$	PhCH=C[C(O)NHPr-*i*]	31	16
$C_{24}H_{26}O_6S_2$	4-MeO-5-$MeC_6H_3CH=C(CO_2Me)$	58	29
$C_{24}H_{28}N_2O_4S_2$	(4-HOC_6H_4)(MeCONEt)C=CH		60
$C_{24}H_{26}O_2S_6$	4-*i*-$PrSC_6H_4C(O)CH=C(SH)$		43
$C_{24}H_{22}N_4O_4S_2$	$EtOC(O)C(NC)=C(NHPh)$	91	22
$C_{24}H_{20}Cl_2N_4O_4S_2$	$EtCO_2C(NC)=C[NH(4-ClC_6H_4)]$	94	22
$C_{24}H_{16}N_2O_4S_4$			133
$C_{24}H_{18}N_4O_2S_4$		79	15, 128
$C_{26}H_{32}N_2O_2S_2$	PhCH=C[C(O)NHPr-*n*]	31	16
$C_{26}H_{34}N_4O_2S_2$	$(Me_2N)_2C=C[C(O)Ph]$	64	47, 48
$C_{26}H_{30}O_2S_6$	4-$Me(CH_2)_3SC_6H_4C(O)CH=C(SH)$		43
$C_{26}H_{26}N_4O_4S_2$	$EtOC(O)C(NC)=C(4-MeC_6H_4NH)$	94	22
$C_{26}H_{32}N_4O_6P_6S_2$	$(EtO)_2P(O)C(NC)=C(NHPh)$	92	42
$C_{26}H_{20}N_2O_4S_4$			133
$C_{26}H_{20}N_2O_4S_4$			133
$C_{26}H_{22}N_4O_2S_4$		74	15, 128
$C_{26}H_{16}N_6O_2S_6$		5	15, 128

Table 1. (continued)

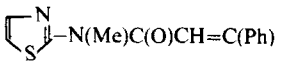
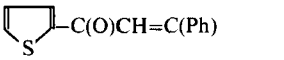
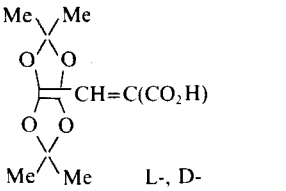
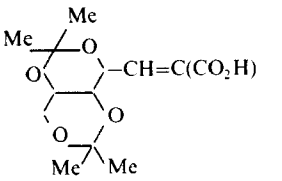
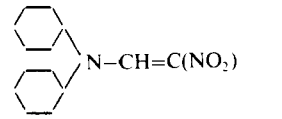
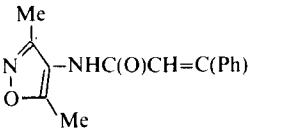
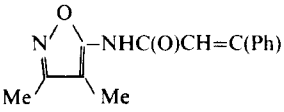
Formula	R	Yield, %	Ref.
$C_{26}H_{22}N_4O_2S_4$		5	15, 128
$C_{26}H_{18}O_2S_4$			134
$C_{26}H_{38}O_{12}S_2$	 L-, D-	99	25, 26
$C_{26}H_{38}O_{12}S_2$		40–55	25, 26
$C_{28}H_{34}O_2S_6$	4-[*i*-Pr$(CH_2)_2$S]C_6H_4C(O)CH=C(SH)		43
$C_{28}H_{36}N_4O_2P_2S_2$	$(EtO)_2$P(O)C(CN)=C(NHC_6H_4Me-4)	90	42, 61
$C_{28}H_{46}N_4O_4S_2$			61
$C_{28}H_{26}N_4O_4S_2$		70	15
$C_{28}H_{26}N_4O_4S_2$		85.6	15
$C_{30}H_{22}O_2S_2$	OHCC(Ph)=C(Ph)		135, 136
$C_{30}H_{26}S_6$	$(Ph)_2$C=C(Me)		73
$C_{30}H_{20}Cl_2S_2$	4-ClC_6H_4C(O)CH=C(Ph)	9	69
$C_{30}H_{20}Cl_2O_2S_2$	4-ClC_6H_4C(O)CH=C(Ph) (*E*,*E*)	61	76
$C_{30}H_{20}Br_2O_2S_2$	4-BrC_6H_4C(O)CH=C(C_6H_4Me-4)	64	39
$C_{30}H_{22}O_2S_6$	PhSC_6H_4C(O)CH=C(SH)		43
$C_{30}H_{26}S_4$	MeSC(Ph)=C(Ph)		66
$C_{30}H_{22}O_2S_2$	PhC(O)CH=C(Ph)	52	137

Table 1. (continued)

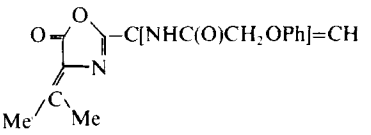
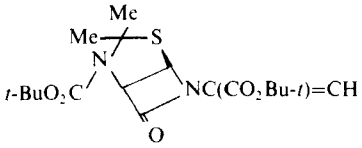
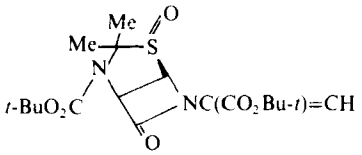
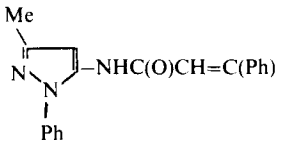
Formula	R	Yield, %	Ref.
$C_{30}H_{22}O_4S_4$	$PhOC_6H_4C(O)CH=C(SH)$		43
$C_{30}H_{20}N_2S_2$	$PhC(NC)=C(Ph)$	83	130
$C_{30}H_{22}N_4S_2$	$PhNHC(Ph)=C(CN)$		36
$C_{30}H_{22}N_4S_2$	$PhN(NC)C(Ph)=CH$	50	138
$C_{30}H_{20}Br_2O_2S_2$	$4\text{-}BrC_6H_4C(O)CH=C(Ph)$	64	38
$C_{32}H_{26}O_2S_2$	$4\text{-}MeC_6H_4C(O)CH=C(Ph)$	61	39
$C_{32}H_{26}O_2S_2$	$PhC(O)CH=C(C_6H_4Me\text{-}4)$	73	39
$C_{32}H_{30}S_4$	$EtSC(Ph)=C(Ph)$		66
$C_{32}H_{30}N_4O_8S_2$			48, 139
$C_{32}H_{24}Br_2O_2S_2$	$4\text{-}BrC_6H_4C(O)CH=C(C_6H_4Me\text{-}4)$	64	137
$C_{34}H_{34}S_4$	$PrSC(Ph)=C(Ph)$		66
$C_{34}H_{30}O_2S_2$	$4\text{-}MeC_6H_4C(O)CH=C(C_6H_4Me\text{-}4)$	77	137
$C_{34}H_{26}O_4S_2$	$(Ph)_2C=C[CH=CHCO_2H]$ (E)	40	34
$C_{34}H_{26}O_4S_2$	$(Ph)_2C=C[CH=CHCO_2H]$ (Z)	71	34
$C_{34}H_{30}O_4S_2$	$4\text{-}MeOC_6H_4C(O)CH=C(C_6H_4Me\text{-}4)$	75	39
$C_{36}H_{30}O_4S_2$	$(Ph)_2C=C[CH=CHCO_2Me]$ (E)		34
$C_{36}H_{30}O_4S_2$	$(Ph)_2C=C[CH=CHCO_2Me]$ (Z)	91	34
$C_{36}H_{22}N_4S_2$	$(CN)_2C=C[(Ph)CH=C(Ph)]$	96	38
$C_{36}H_{54}N_4O_{10}S_4$			49
$C_{36}H_{54}N_4O_{12}S_4$			49
$C_{38}H_{32}N_6O_2S_2$		50	15

Table 1. (continued)

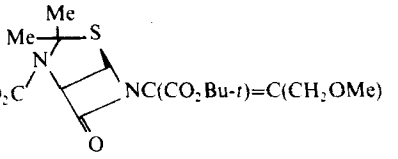
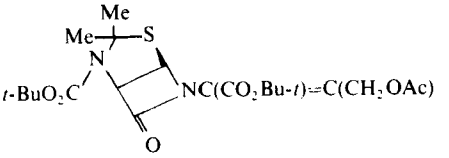
Formula	R	Yield, %	Ref.
$C_{40}H_{62}N_4O_{12}S_4$			49
$C_{40}H_{30}S_2$	$(Ph)_2C{=}C(Ph)$	31	37
$C_{42}H_{62}O_2S_6$	$Me(CH_2)_{11}SC_6H_4C(O)CH{=}C(SH)$		43
$C_{42}H_{62}N_4O_{14}S_4$			49
$C_{44}H_{38}O_4S_2$	$(4\text{-}MeOC_6H_4)_2C{=}C(Ph)$		37
RSS(O)R			
$C_{40}H_{30}OS_2$	$(Ph)_2C{=}C(Ph)$	30	37
$C_{44}H_{38}O_5S_2$	$(MeOC_6H_4)_2C{=}C(Ph)$		37

Table 2. Nonsymmetrical divinyl disulfides, RSSR′

Formula	R, R′	Yield, %	Ref.
$C_{11}H_{13}N_3OS_3$	(NC)C(Me)=CH, (NC)C(Me)=C[SC(O)N(Me)$_2$]		62
$C_{13}H_{18}N_2O_2S_5$	($EtCO_2$)C(NC)=C(SMe), ($EtCO_2$)C(SNH_2)=C(SMe)	17	44
$C_{13}H_{12}ClNO_8S_3$	($MeCO_2$)C(Cl)=C(CO_2Me), ($MeCO_2$)C(SCN)=C(CO_2Me)	60	54, 55
$C_{17}H_{25}N_3OS_3$	(*t*-Bu)C(NC)=CH, (*i*-Pr)C(NC)=C[SC(O)N(Me)$_2$]	10	62

Table 3. Divinyl tri- and polysulfides[67] RS_xR

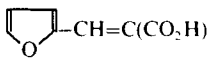
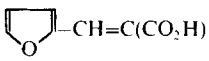
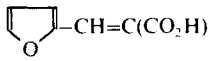
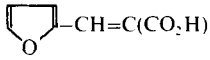
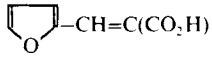
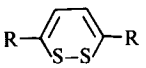
Formula	x	R	Yield, %
$C_{12}H_{18}S_3$	3		33
$C_{12}H_{18}S_4$	4		~90
$C_{14}H_{26}S_3$	3	EtCH=C(Pr-*n*)	31
$C_{14}H_{26}S_4$	4	EtCH=C(Pr-*n*)	~90
$C_{14}H_{10}O_6S_3$	3		85
$C_{14}H_{10}O_6S_4$	4		83
$C_{14}H_{10}O_6S_5$	5		75
$C_{14}H_{10}O_6S_6$	6		63
$C_{14}H_{10}O_6S_7$	7		60
$C_{18}H_{14}O_4S_3$	3	PhCH=C(CO_2H)	80
$C_{18}H_{14}O_4S_4$	4	PhCH=C(CO_2H)	75
$C_{18}H_{14}O_4S_5$	5	PhCH=C(CO_2H)	69
$C_{18}H_{14}O_4S_6$	6	PhCH=C(CO_2H)	53
$C_{18}H_{14}O_4S_7$	7	PhCH=C(CO_2H)	46
$C_{22}H_{18}O_4S_3$	3	PhCH=CHCH=C(CO_2H)	72
$C_{22}H_{18}O_4S_4$	4	PhCH=CHCH=C(CO_2H)	75
$C_{22}H_{18}O_4S_5$	5	PhCH=CHCH=C(CO_2H)	62
$C_{22}H_{18}O_4S_6$	6	PhCH=CHCH=C(CO_2H)	65
$C_{22}H_{18}O_4S_7$	7	PhCH=CHCH=C(CO_2H)	58
$C_{40}H_{30}S_3$	3	PhCH=C(Ph)	77
$C_{40}H_{30}S_4$	4	PhCH=C(Ph)	68
$C_{40}H_{30}S_5$	5	PhCH=C(Ph)	52
$C_{40}H_{30}S_6$	6	PhCH=C(Ph)	55
$C_{40}H_{30}S_7$	7	PhCH=C(Ph)	49

Table 4. Divinyl disulfides, derivatives of 1,2-dithiin[132]



Formula	R	m.p., °C [b.p., °C/mm Hg]	UV, λ_{max} nm (lg ε)
$C_4H_4S_2$	H	[45/4]	451 (2.88)
$C_{12}H_8S_4$	2-Thienyl	123	481 (3.76)
$C_{16}H_{12}S_2$	Ph	143	468 (3.12)
$C_{18}H_{28}S_2$	4-MeC_6H_4	162	470 (3.46)
$C_{18}H_{28}O_2S_2$	4-MeOC_6H_4	179	467 (4.43)

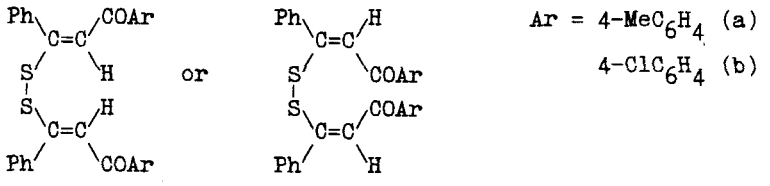
The structures of all known divinyl disulfides, with yields and relevant references are listed in Tables 1–4.

3. PROPERTIES OF DIVINYL DISULFIDES

3.1. Physico-Chemical Properties

The physico-chemical properties of divinyl disulfides have not been systematically studied. Their b.ps, m.ps and spectra (mass, NMR, IR, UV) are scattered over the corresponding synthetic papers. Most of these data are briefly collected in Table 5.

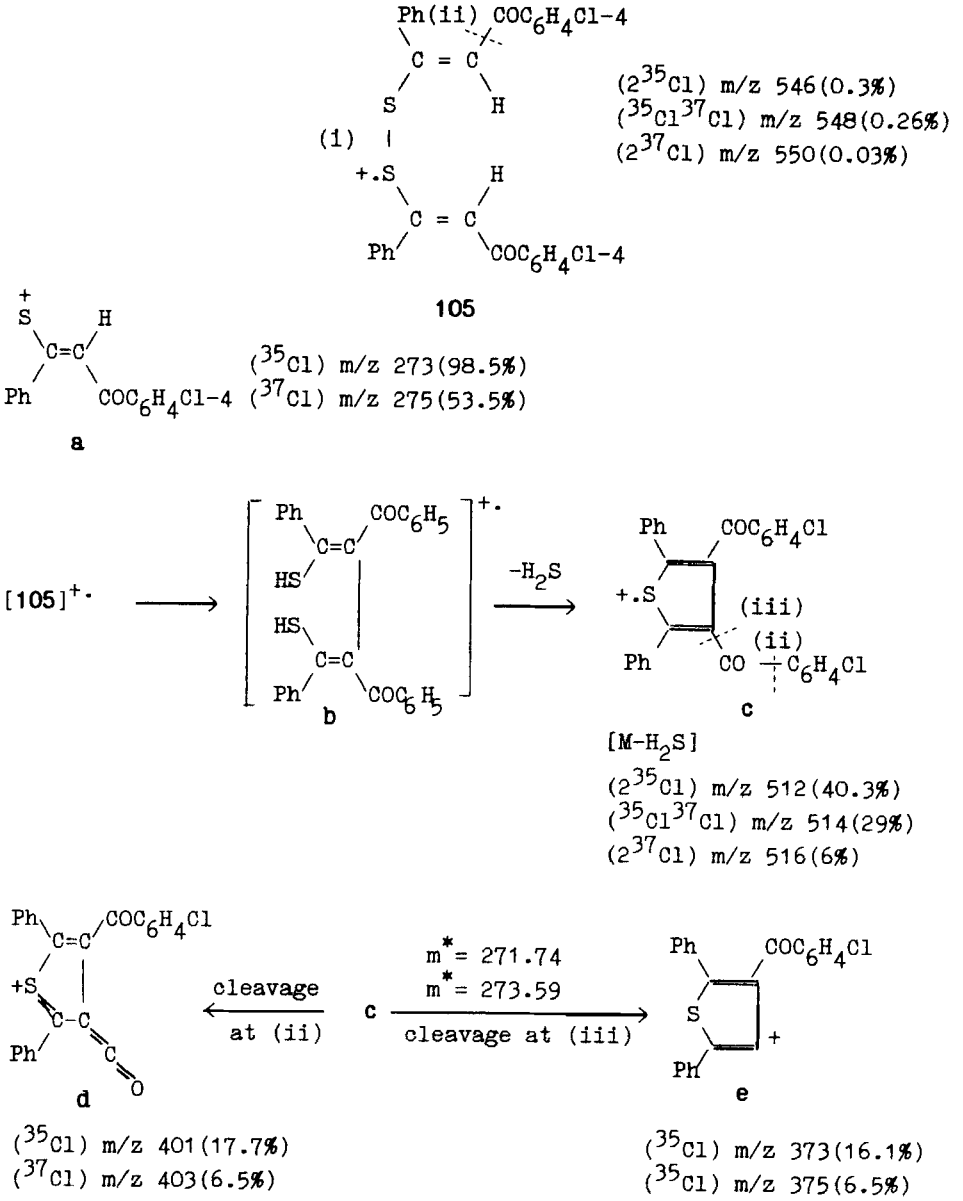
In[68,69] the mass spectra of the (*Z*,*Z*)- or (*E*,*E*)-β,β′-di(α-aroylstyryl) disulfides **105** are discussed.



105

The fragmentation patterns support their proposed structure and configuration.

The mass spectra of the disulfides **105** give a molecular ion which appears as a triplet at *m*/*z* 546, 548 and 550, corresponding to species containing the appropriate combinations of ^{35}Cl and ^{37}Cl. The 4-chlorobenzoyl cation which appears as a doublet at *m*/*z* 139 (100%) and 141 (48.4%) is considered to be good evidence for the proposed structure. The low abundance of the molecular ion indicates that it is highly unstable. It appears to lose an electron from the neutral sulfur atom, followed by homolytic cleavage of the S–S bond to give the very abundant fragment ion **a**, which appears as a doublet at *m*/*z* 273 (98.5%) and 275 (53.5%). The appearance of a triplet at *m*/*z* 512/514/516, $[M-H_2S]^{+\cdot}$, which corresponds to the radical ion **c**, supports the *E*,*E*-configuration rather than the *Z*,*Z*-configuration, since such an ion is supposed to result from rearrangement reactions which finally give the dithiol radical ion **b**. Subsequent loss of H_2S gives the thiophene radical ion **c**. For steric reasons such a reaction is more feasible if the compound has the *E*,*E*-configuration. It may be argued that the driving force for this reaction may be associated with the reasonance stabilization of the substituted thiophene structure and also with the thermodynamic stability and the high ionization potential of the neutral fragment (H_2S).[70] The radical ion **c** either loses a chlorophenyl radical [cleavage at (ii)] to give ion **d** or a 4-chlorobenzoyl cation [cleavage at (iii)] to produce ion **e**.



Scheme 50

The infrared spectra of the divinyl disulfides **105** (**a** and **b**) show strong bands at 1632 and 1640 cm^{-1} ($\nu_{C=O}$), respectively. The appearance of one band for C=C indicates that they are stereochemically identical, i.e., both compounds should have either the *E,E*- or the *Z,Z*-configuration. The ν_{C-S} for both compounds appears as a weak band at 645 and 635 cm^{-1}, respectively.[68,71]

Table 5. Properties of divinyl disulfides, RSSR

R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
CH_2=CH	38–42/10 n_D^{20} 1.561	^{1}H NMR: 5.3 d, 5.45 d, 6.3 dd, J = 9.5 Hz, 15.5 Hz	9, 163
ClCH=CCl	85–90/0.025 105–115/0.5–0.7, n_D^{20} 1.6371	IR: 1560, 920	50
Cl_2C=CH	85–87/0.05 n_D^{20} 1.6202		50
MeCH=CH	78–84/10 n_D^{20} 1.5528	MS: 146 (2.5), 111 (100), 112 (65), 97 (42), 45 (37), 77 (22), 34 (22), 39 (19), 27 (13), 67 (13), 71 (11) ^{1}H NMR: 1.75 t, 5.7 t, 6.92 t	9
Me_2C=C(Me)		MS: 202, 85, 69 ^{1}H NMR: 1.77 s, 1.96 s, 2.00 s	70, 121
MeCH=C(MeC=CH_2)		MS: 254 ^{1}H NMR ($CDCl_3$): 1.78 s, 1.83 s, 1.95 s, 4.75 m, 5.13 m ^{13}C NMR ($CDCl_3$): 142.3, 136.1, 133.3, 116.6, 23.0, 22.2	58, 59
$(Me)_2$C=C(SBu-*t*)		MS: 350, 143 (31), 119 (15), 87 (26), 86 (18), 85 (11), 57 (100) ^{1}H NMR: 2.15 s, 2.12 s, 1.37 s ^{13}C NMR: 155.3 s, 125.5 s, 48.1 s, 31.4 q, 25.6, 24.3 q IR: 3000, 2960, 2935, 2895, 2860, 1568, 1470, 1453, 1430, 1390, 1363, 1070, 880	126
$(CF_3)_2$C=C(CF_3)	74–76/8	IR: 1600	13
4-MeC_6H_4C(O)CH=C(Me)	164–165	^{1}H HMR ($CDCl_3$): 2.39 s, 2.41 s, 7.20 s IR (KBr): 1635, 1605 UV (CH_2Cl_2): 275 (4.24),[a] 334 (4.55)	137
4-MeOC_6H_4C(O)CH=C(Me)	148–150	^{1}H NMR: 2.39 s, 3.82 s, 7.22 s IR: 1627, 1599 UV: 295 (4.33), 339 (4.77)	137
PhC(O)–CH=C(Me)	149–150	^{1}H NMR: 7.06 s IR: 1632, 1597 UV: 267 (4.12), 336 (4.23)	137
4-BrC_6H_4C(O)CH=C(Ph)	200–202	^{1}H NMR: 6.98 s IR: 1638, 1583 UV: 280 (4.38), 341 (4.37)	137

Table 5. (continued)

R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
4-$MeC_6H_4C(O)CH=C(Ph)$	177–179	^1H NMR: 2.36 s, 6.99 s IR: 1630, 1608 UV: 280 (4.37), 338 (4.46)	137
$PhC(O)CH=C(C_6H_4Me$-4)	127–128	^1H NMR: 2.10 s, 7.00 s IR: 1630, 1590 UV: 267 (4.34), 339 (4.43)	137
4-$BrC_6H_4C(O)CH=C(C_6H_4Me$-4)	209–210	^1H NMR: 2.16 s, 6.97 s IR: 1639, 1591 UV: 279 (4.32), 343 (4.37)	137
4-$MeC_6H_4C(O)CH=C(C_6H_4Me$-4)	178–180	^1H NMR: 2.10 s, 2.40 s, 7.00 s IR: 1634, 1605 UV: 290 (4.34), 340 (4.42)	137
4-$MeOC_6H_4C(O)CH=C(C_6H_4Me$-4)	158–160	^1H NMR: 2.19 s, 3.90 s, 6.98 s IR: 1638, 1602 UV: 297 (4.34), 343 (4.56)	137
$(Ph)_2C=C[CH=CHCO_2H]$	207–208 (*Z*) 248–252 (*E*)	^1H NMR: 6.72, 5.62, J = 11.5 Hz, 7.48, 6.39, J = 15 Hz IR: 3000, 1693, 1631, 460	34
$(Ph)_2C=C[CH=CHCO_2Me]$	75–78 (*Z*) 165–166 (*E*)		34
$PhC(O)N(Me)C(Me)=CH$	165–166		21
$PhCH_2N(CHO)C(Me)=C(Me)$	resin	^1H NMR ($CDCl_3$): 7.47 s, 5.20, 4.33 q, 2.06 s, 1.97 s, 1.72 s, J = 15 Hz	32
$(CHO)C(Ph)=C(Ph)$	199–201	IR: 1675	135, 136
$PhCH=C(CNHMe)$	138	^1H NMR: 2.0 s, 6.68 m, 8.82 m IR: 3240, 1620	16
$PhCH=C(CNHEt)$	158		16
$PhCH=C(CNHPr$-*n*)	120		16
$PhCH=C(CNHPr$-*i*)	153		16
$PhCH=C(CNHBu$-*n*)	116		16
$[(Me)_2N]_2C=C(CO_2Me)$	163–164	MS: 406, 235, 203 ^1H NMR: 3.57 s, 2.95 s, 4.07 g IR: 1640, 1515, 1057, 767	47
$[(Me)_2N]_2C=C(CO_2Et)$	142–143	MS: 407.171, 203.086 ^1H NMR: 1.23 t, 2.96 s, 4.07 g IR: 1633, 1510, 1050, 766	47
$(Me_2N)_2C=C(CO_2Ph)$	192–195	^1H NMR: 2.85 s, 7.2–7.6 m IR: 1600, 1590, 1510, 1400, 710, 660	47

Table 5. (continued)

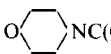
R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
4-$MeC_6H_4C(O)CH=C(Ph)$	174–175	MS: 547	69
4-$ClC_6H_4C(O)CH=C(Ph)$	170–171		69
t-BuCH=CH (*E,E*) (*E,Z*)	70	MS: 230 (49), 215 (15), 174 (8), 116 (11), 115 (15), 113 (10), 103 (11), 101 (32), 100 (8), 99 (89), 85 (13), 83 (100), 81 (30), 79 (10), 73 (12), 67 (22), 65 (12), 62 (11), 59 (52), 57 (47), 55 (63), 53 (18), 47 (10), 45 (50), 44 (71), 43 (40), 41 (93), 39 (37) ^{1}H NMR: 5.9 m, 1.0 s, 1.4 s IR: 620, 778, 802, 822, 914, 948, 1028, 1230, 1255, 1293, 1355, 1383, 1453, 1465, 1608, 1706, 2980, 3018 UV: 214 (67.5)	63
4-$MeC_6H_4C(O)CH=C(Me)$	164–165	^{1}H NMR: 2.39, 2.41, 7.10 IR: 1635, 1605 UV: 275, 334	39
4-$MeOC_6H_4C(O)CH=C(Me)$	148–150	^{1}H NMR: 2.39, 2.82, 7.22 IR: 1627, 1599 UV: 295, 339	39
MeSC(Ph)=C(Ph)	153–155	UV: 318 (3.98), sh 372	66
EtSC(Ph)=C(Ph)	107	UV: sh 275, 348 (3.56)	66
PrSC(Ph)=C(Ph)	oil		66
$PhCH_2SC(Ph)=C(Ph)$	184	UV: sh 307, 328 (4.02)	66
(4-$MeOC_6H_4$)C=C(Ph)	175		37
$MeO_2CC(HNAc)=CH$	202.5–204	^{1}H NMR: 7.96 s, 7.59 s, 3.48 s, 1.87 s	51
$MeO_2CC(Cl)=C(CO_2Me)$	152		54, 55
	70–72		54, 55
$MeO_2CC(NCS)=C(CO_2Me)$	124–125	IR: 2160, 1730	54, 55
2-$BrC_6H_4HC=C(CO_2H)$	206–207		28
2-$ClC_6H_4HC=C(CO_2H)$	190–191		27
2-$MeOC_6H_4C(Me)=C(CO_2H)$	197–199	MS: 446 ^{1}H NMR: 2.19 s, 3.73 s, 6.68–7.04 m, 7.11–7.34 m	31
3-Me-4-$MeOC_6H_3CH=C(CO_2H)$	211–212	^{1}H NMR: 2.23 s, 3.78 s, 3.91 s, 6.91 d, J = 9 Hz; 7.77 s, 7.82 d, J = 9.Hz; 7.97 s	29
3-Me-4-$MeOC_6H_3CH=C(CO_2CH_3)$	96–97		29
3-MeO-4-$MeC_6H_3CH=C(CO_2H)$	216	^{1}H NMR: 7.90, 7.28, 7.60	29

Table 5. (continued)

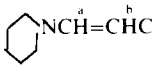
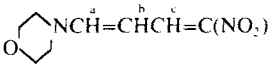
R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
4-$MeOC_6H_4CH$=$C(CO_2Me)$	155–157	^{1}H NMR: 7.75, 5.7–7.0, 3.80 IR: 1690	131
PhCH=C(SMe)	174	^{1}H NMR: 2.30, 5.42, 6.77–7.02 IR: 700, 1455, 1500, 2920, 3020	23
$Me_2N\overset{a}{C}H=\overset{b}{C}H\overset{c}{C}H=C(NO_2)$	144	^{1}H NMR: 7.88 (a), 5.48 (b), 8.22 (c), 3.20, 2.97 IR: 1620, 1562, 1544, 1435, 1415, 1340, 1300, 1260, 1200, 1175, 1106, 995	123
$Et_2N\overset{a}{C}H=\overset{b}{C}H\overset{c}{C}H=C(NO_2)$	138	^{1}H NMR: 7.88 (a), 5.60 (b), 8.28 (c), 1.20, 1.15 IR: 1610, 1545, 1440, 1345, 1305, 1260, 1190, 1123, 1100, 1080, 1005, 985	123
$Pr_2N\overset{a}{C}H=\overset{b}{C}H\overset{c}{C}H=C(NO_2)$	154	^{1}H NMR: 7.86 (a), 5.60 (b), 8.24 (c), 1.58, 0.84 IR: 1614, 1603, 1554, 1539, 1440, 1427, 1349, 1300, 1260, 1180, 1168, 1130, 1102, 1025, 987	123
	158	^{1}H NMR: 7.88 (1), 5.62, (b), 8.25 (c), C_5H_{10}-broad peak IR: 1610, 1555, 1538, 1425, 1352, 1300, 1270, 1260, 1172, 1158, 1129, 1038, 1000, 985	123
	160	^{1}H NMR: 7.88 (a), 5.63 (b), 8.26 (c), C_4H_8-broad peak IR: 1605, 1557, 1545, 1455, 1435, 1335, 1298, 1270, 1250, 1170, 1110, 1018, 980	123
$H_2NC(O)CH$=CH (*Z*,*Z*) and (*Z*,*E*)	153–154		87
EtNHC(O)CH=CH (*Z*,*Z*)	176–177 (168–170)		87
$H_2NC(O)C(Br)$=CH (*E*,*E*)	173–175 (172–173)		87
PhC(NC)=C(Me)	129.5		130
PhC(NC)=C(Ph)	151–153		130
PhNHC(Ph)=C(CN)	230–231	IR: 3300, 3250, 2180, 1580, 1545 UV: 265, 325, 385	36
PhNHC(Me)=C(CN)	215–216	IR: 3220, 2180, 1560, 1540 UV: 275, 295, 355	36
$EtO_2CC(NC)$=C(SMe)	136–137	^{1}H NMR: 10.70, 9.68, 4.40, 4.38, 3.98, 3.96, J = 7.5 Hz UV: 224, 240, 294, 334	44

Table 5. (continued)

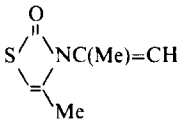
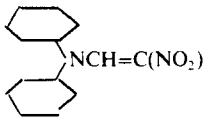
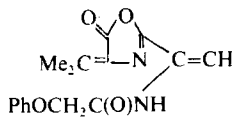
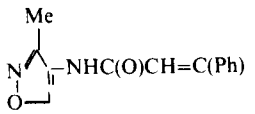
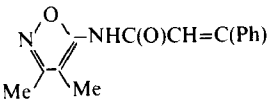
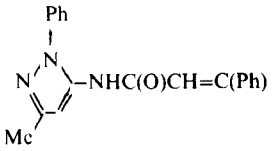
R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
$MeC(O)C(NC)=C(NH_2)$	178–180	IR: 1660, 2200, 3290, 3360 UV: 250, 266, 292	41
$(NC)_2C=C(Ph)CH=C(Ph)$	254	MS: 576 IR: 1366, 1409, 1489, 1528, 1570, 2200	38
$PhC(O)C(NC)=C(SMe)$	220–222	IR: 1600, 1714, 2215	45
$(EtO)_2P(O)C(NC)=C(NHPh)$	136	IR: 1210–1220, 2190, 3150	42
$(EtO)_2P(O)C(NC)=$ $=C[NHC_6H_4Me\text{-}4]$	127		42
$PhN(NC)C(Ph)=CH$	141–142	MS: 476 IR: 2210 UV: 280	138
	132–133	^1H NMR: 2.04, 5.85, 6.55 IR: 2450	33
	200 (decomp.)	^1H NMR: 0.8–2.0, 3.23, 4.90, 8.73	61
	135–138	IR: 1515, 1600, 1668, 1695, 1790 UV: 332, 375	48
	121–123		15
	200–201 (decomp.)		15
	138–140		15

Table 5. (continued)

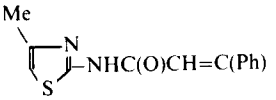
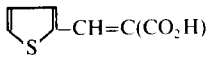
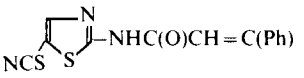
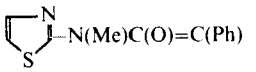
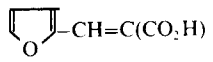
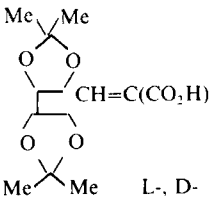
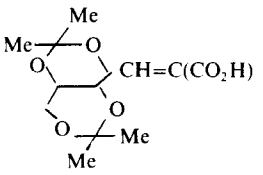
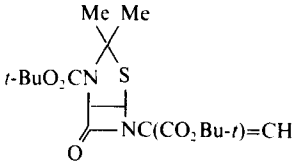
R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
	138–141		15
	179–180		15
	215		77
	215–217		1, 128
	141–142		15, 128
	215		124, 125
 L-, D-	syrup	IR (film): 1660, 1730	25, 26
	caramel	IR: 1635, 1685, 1700, 2500–3300	25, 26

Table 5. (continued)

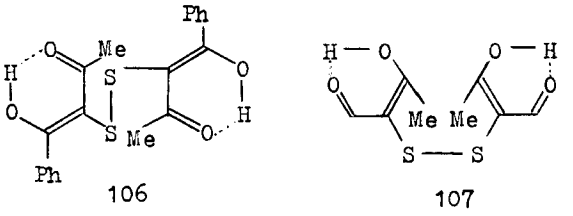
R	m.p., °C b.p., °C/mm Hg	Spectra	Ref.
$Et_2NC(Cl)=C(Me)$	37–38		52
		UV: 317	49

[a] In brackets: log ε values.

The NMR spectrum of **105** also supports the symmetrical configuration of this compound. Thus, the signal for the two olefinic protons appears as a singlet at δ 7.0 ppm, which indicates that they are magnetically equivalent.

The electronic spectra of **105** (**a** and **b**) are identical and show two maxima at 346 nm (ε = 16.87), 267 nm (ε = 22.19), and 335 nm (ε = 21.90), 274 nm (ε = 22.45), respectively.[68]

The crystal structure of the enol form of 1,1′-diphenyl-2,2′-dithiobis(butane-1,2-dione), i.e., the divinyl disulfide **106** (Scheme 51) has been determined by X-ray diffraction methods.[72] The butane-1,3-dione groups are planar and the phenyl groups lie twisted 47.8 and 50.3° with respect to these planes. The distances between the oxygen atoms within the butanedione groups are 2.374 and 2.436 Å, indicating strong intramolecular hydrogen bonds. The compound is, in fact, better named 3,3′-dihydroxy-3,3′-diphenyl-2,2′-dithio-bis-but-2-en-1-one. The S–S bond length is 2.078 ± 0.005 Å and the dihedral angle C–S–S–C is 66.4°.



106 107

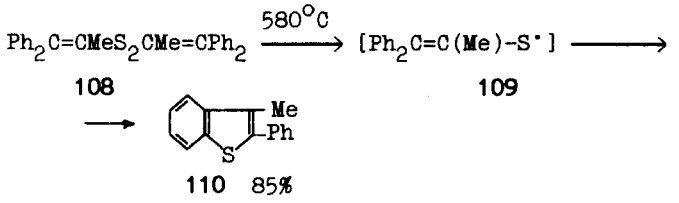
Scheme 51

The same authors[68] have determined the crystal structure of the enol form of disulfide **107**, actually a divinyl disulfide (Scheme 51) from three-dimensional X-ray diffraction data. The molecule exists as the enol tautomer and the short intramolecular hydrogen bonds formed [O···O contacts of 2.418 and 2.444 Å] are asymmetric. There is evidence for alternating single and double bonds in the enol ring. The S–S distance is 2.082 Å and the C–S distances 1.744 and 1.743 Å. From comparison with other organic sulfides, a dependence of the C–S bond length on the hybridization of the carbon atom is indicated. The C–S–S–C torsion angle is 68.6°.

3.2. Reactions

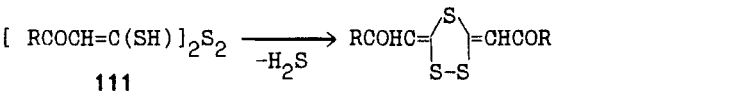
3.2.1. Thermal rearrangements. Upon heating divinyl disulfides can undergo rearrangement to bisdithio esters and thiophene derivatives. In this way, methyl dithiopropionate, methyl phenyldithioacetate, 2,5-bis(methylthio)-3,4-dimethylthiophene, and 2,5-bis(methylthio)-3,4-dithienylthiophene have been prepared.[73]

In the pyrolysis of the divinyl disulfide **108** intramolecular cyclization of styrylthiyl radicals **109** to give the benzothiophenes **110** in 42–85% yield was mainly observed.[73]



Scheme 52

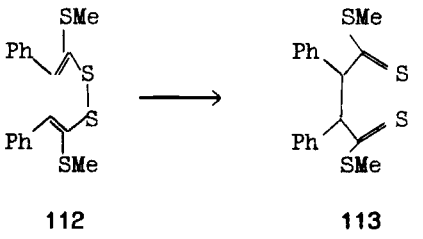
Upon heating of the divinyl disulfides **111**, hydrogen sulfide is eliminated and cyclization occurs.[43]



R = Ph, 3-ClC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$; 2,4-(MeO)$_2$C$_6$H$_3$;
PhOPh, 4-MeSC$_6$H$_4$, 4-EtSC$_6$H$_4$, 4-i-PrC$_6$H$_4$,
4-(CH$_2$)$_3$MeSC$_6$H$_4$, 4-(CH$_2$)$_2$CHMe$_2$SC$_6$H$_4$, 4-(CH$_2$)$_{11}$MeSC$_6$H$_4$

Scheme 53

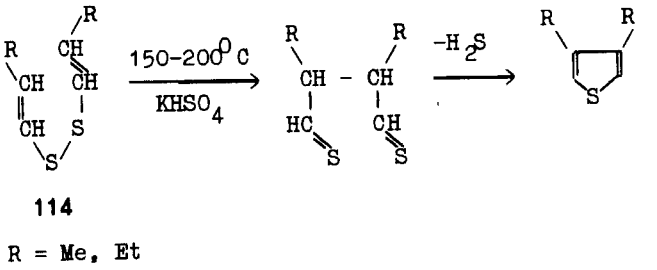
The sigmatropic rearrangement of **112** to **113** has been reported in:[74]



112 113

Scheme 54

3,4-Dialkylthiophenes have been prepared in good yields by heating of di(1-alkenyl) disulfides **114** at 150–100 °C in the presence of potassium hydrogen sulfate.[75]

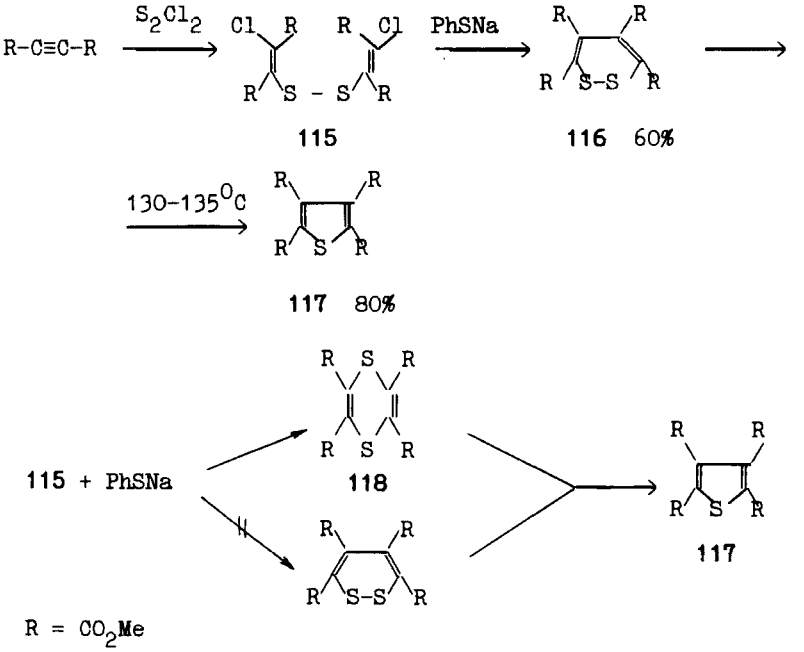


114

R = Me, Et

Scheme 55

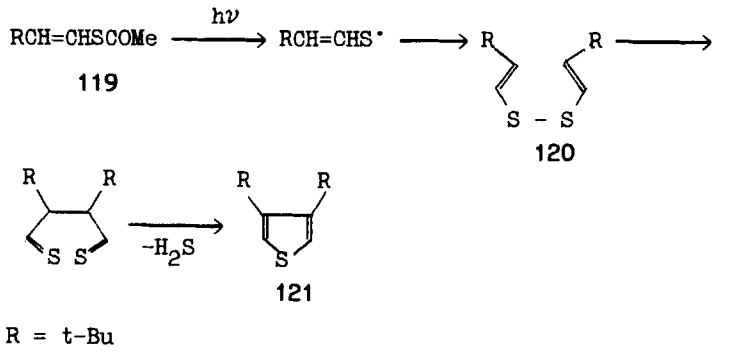
The dithiins **116**, obtained from the bis(2-chlorovinyl) disulfides **115**, have been reported to yield the thiophenes **117** upon heating.[55] Reinvestigation[54] of this reaction demonstrated that the product obtained upon treatment of the disulfide with sodium benzenethiolate was, in fact, the 1,4-derivative **118**.



Scheme 56

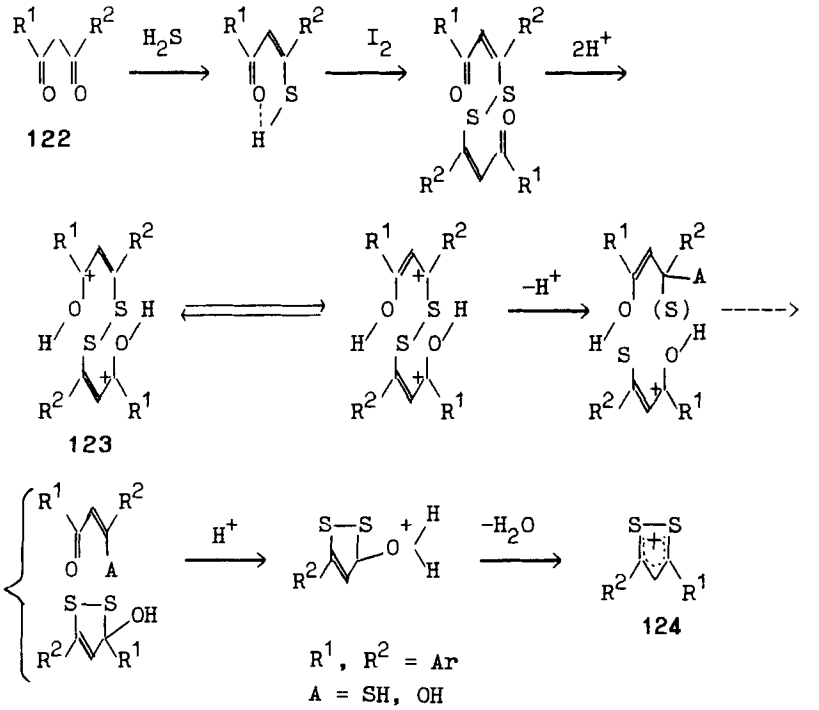
Presumably the elemental analysis and the observation that sulfur is thermally extracted to give the thiophene **117** were the motivation for the assignment of the structure as a 1,2-dithiin. However, both 1,2- and 1,4-dithiins release sulfur upon heating to provide the corresponding thiophenes.[54]

3.2.2. Photolysis. The divinyl disulfides **120**, formed during the photolysis of the *S*-vinyl thioacetates **119** by dimerization of the corresponding enethiyl radicals, further undergo Cope rearrangement to give the thiophenes **121** with loss of H_2S.[63]



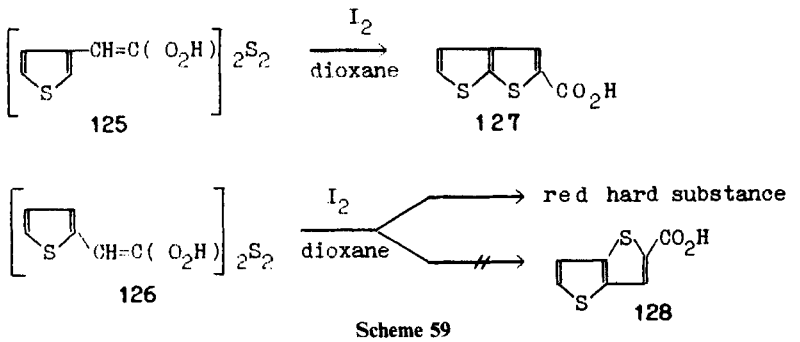
Scheme 57

3.2.3. Reactions of functional groups. The disulfides **123**, prepared from the diketones **122** by successive treatment with hydrogen sulfide and iodine under the action of acids, form the thiolium cations **124**.[76]



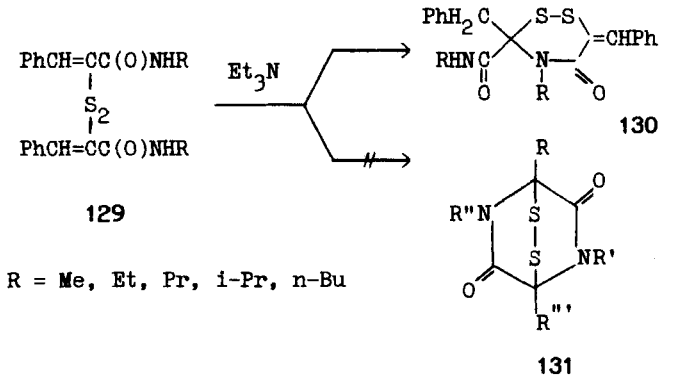
Scheme 58

When treated with iodine in dioxan, the disulfide **125** gives thieno[2,3-*b*]thiophene-2-carboxylic acid **127**, whereas the isomeric disulfide **126** is converted to an unidentified red solid more quickly than to the expected thieno[3,2-*b*]thiophene-2-carboxylic acid **128**.[77]



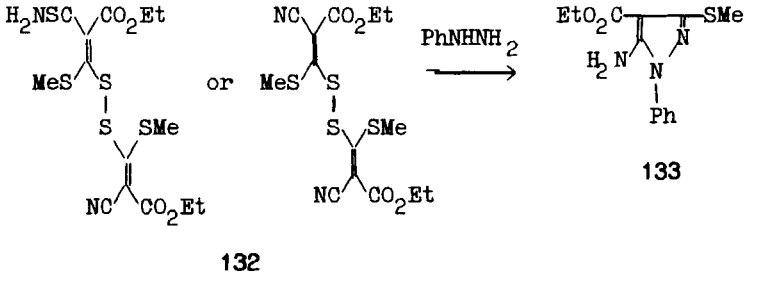
Scheme 59

Since some antibiotics (e.g., glyotoxin and sporidesmin) contain a 3,6-epidithio-2,5-dipiperazinedione structure, an attempt has been made[16] to synthesize compounds of this kind by cyclization of the divinyl disulfides **129** under the action of triethylamine. As a result the dithiazine derivative **130** have been isolated. The expected piperazinedione **131** was not found.



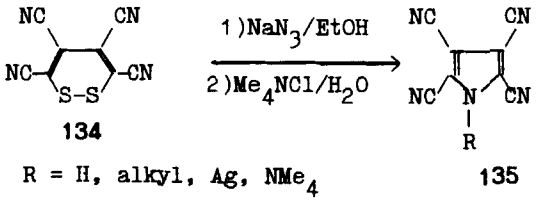
Scheme 60

When heated with phenylhydrazine, the divinyl disulfide **132** forms 5-amino-4-(ethoxycarbonyl)-3-(methylthio)-1-phenyl-1,2-pyrazole **133**.[44]



Scheme 61

The cyclic divinyl disulfide **134** reacts with sodium azide to form the pyrrole **135**.[78]



Scheme 62

3.3. Applications

3.3.1. Biological activity. Divinyl disulfides have, in addition to their irritant action, a toxic effect on the liver and kidneys. A provisional operational limit for divinyl disulfide was set at 2 ppm.[79,163]

The divinyl disulfides $(MeCH{=}CH)_2S_2$ (*E,E*- and *Z,Z*-isomers) have been found by GLC in onion etheric oil.[9,80-82]

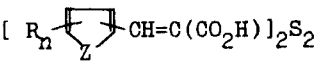
Garlic extract contains the divinyl disulfide $[EtCO_2(CH_2)_3SCH_2CH{=}CH]_2S_2$.[83] This compound as well as di(1-propenyl) disulfide are antithrombotic agents.

The disulfide derivatives of α,α-dithio-β-acrylic acids and salts thereof are recommended for treating extra stress[84-86] and heavy-metal poisoning. On prolonged storage of the onion etheric oil in which divinyl disulfides are found, the content of trisulfides increases, i.e., degradation occurs (possibly due to the presence of water and elevated temperatures). It is better to keep the onion etheric oil in ethanol.[84].

The occurrence of di(1-propenyl) disulfides in volatile sulfur-containing compound mixtures enzymatically produced from caucas (*A. victorialis*) has been established (caucas is one of the garlic-like *Allium* species). 3,4-Dihydro-3-vinyl-1,2-dithiin and 2-vinyl-4*H*-1,2-dithiin, which have antithrombotic activity, have also been isolated from caucas and identified by IR, NMR, and mass spectrometry.[9,80,81]

Disulfides $[R^1C(CN){=}C(NR^2R^3)]_2S_2$ [R^1 = CN, $CONH_2$, CONHMe, CO_2R^2; R^2 and R^3 = H, C_{1-5} alkyl; or (R^2R^3N) = piperidino, pyrrolidino, or morpholine] have been recommended as fungicides, herbicides, or defoliants at 3–30 kg/ha.[17-20]

Dithiobis(β-substituted acrylic acids) and their salts are antihypertensives. Thus, after a single oral dose of 50 mg/kg of α,α′-dithiobis[β-(2-furyl)acrylic acid] given to spontaneously hypertensive rats, systolic blood pressure decreased 19.3, 48.9, 39.6 and 34.8 mm Hg after 4, 34, 48, and 72 h, respectively.[84]



Z = C, O, S, NH ;
R = H, Me, Et, OH, MeO, EtO, Cl, Br, CF_3;
n = 1-3

These divinyl disulfides have also been recommended for enhancing serum and tissue zinc concentrations.[85,86]

The divinyl disulfides $[(RNHCO)(Z)C{=}C(Z')]_2S_2$ (Z=Z'=O, Br, Cl, akyl) exhibit biological activity, particularly in the control of microorganisms. For example, they are useful as bactericidal, fungicidal, and algicidal agents.[87]

3.3.2. Technical application. Bis-(chloroaminoalkenyl) disulfides $[(Et)_2N{-}CCl{-}C(Me)]_2S_2$ have found use as vulcanization accelerators.[52]

Dithiodimaleic acid $[HCO_2CH{=}C(CO_2H)]_2S_2$ is used as an additive to improve nickel-melting baths.[88]

Bis(3-chlorobutenyl) disulfide $[MeCHClCH{=}CH]_2S_2$ has been tested as run-in additive to lubricating oils. This divinyl sulfide has been found to decrease initial wear and to improve the run-in quality of engine parts.[89]

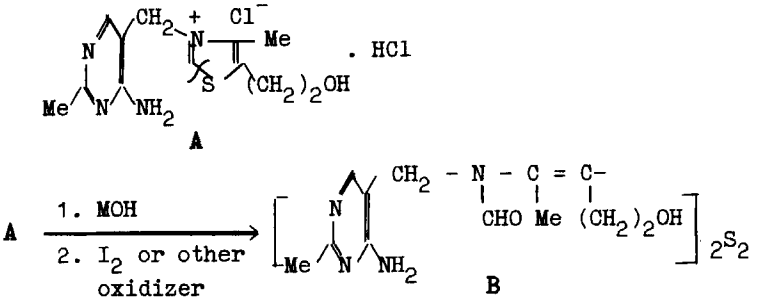
The addition of phenolic compounds such as $2,6\text{-}(Me_3C)_2C_6H_3OH$ and of the disulfide $[CH_2{=}C(Me)]_2S_2$ improves the oxidative stability of lubricating oil. The additive is introduced in an amount of 0.25–2 wt % to a paraffin neutral lubricating oil.[90]

Divinyl disulfide $[CH_2{=}CH]_2S_2$ has been recommended as a thickening agent for preparing sulfur foam.[91,163] Solid sulfur foam is formed by heating sulfur above its m.p., adding a stabilizer and a substance to increase the viscosity, formation of bubbles in the melt, and fast cooling of the mixture below the m.p. of sulfur.

4. DIVINYL DISULFIDES, DERIVATIVES OF THIAMINE (VITAMIN B_1)

4.1. Synthesis

Divinyl disulfides of a special group are derivatives of thiamine (vitamin B_1) (**A**), and prepared from **A** by cleavage with MOH (M = Li, Na, K). Then the thiol function formed by opening of the thiazole ring is oxidized with an appropriate oxidizer, I_2/NaI, H_2O_2, or $K_3Fe(CN)_6$, to afford the thiamine disulfide **B**.[92]



Scheme 63

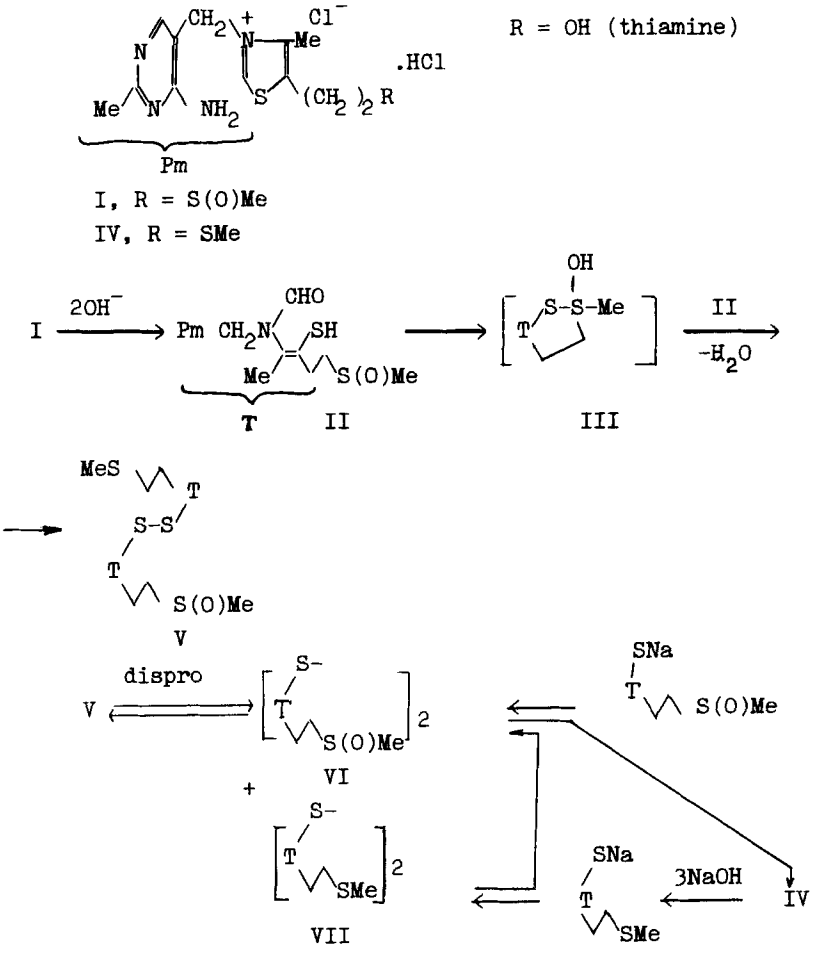
The known representatives of this group of divinyl disulfides are presented in Tables 5–10.

Consequently, two groups of synthetic methods leading to divinyl disulfides of the type **B** exist:

1. Methods based on reaction of thiamine chloride **A** (or the corresponding acetyl or anhydride derivative) with NaOH and $Na_2S_4O_6$, H_2S, or MeC(O)SH.[93–98]

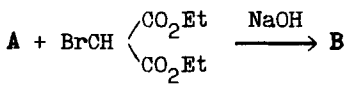
2. Methods based on the modification of thiamine disulfide **B** with reagents attacking mainly the $(CH_2)_2OH$ function (AcCl, BzCl, $PhSO_2Cl$, anhydrides, $Na_2S_2O_3$) or the formation of salts and complexes (carboxylic and mineral acids and the like).[99-105]

The following transformations of thiamine and its derivatives have been reported:[93]



Scheme 64

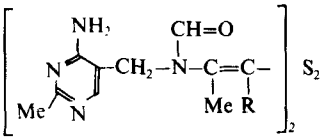
Reaction of thiamine **A** with diethyl bromomalonate gives the symmetrical disulfides **B** in high yields.[98]



Scheme 65

Treatment of thiamine disulfide with C_{12-18} fatty acids leads to the formation of adducts (~95% yield).[99]

Table 6. Symmetrical divinyl disulfides, derivatives of thiamine



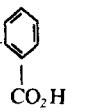
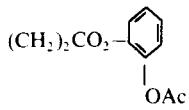
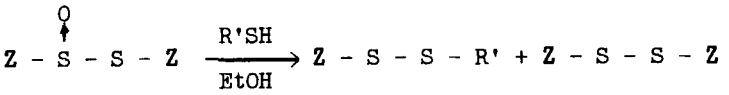
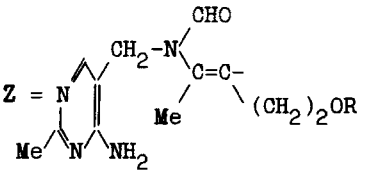
Formula	R	Yield, %	m.p., °C	Ref.
$C_{20}H_{26}N_8O_2S_2$	H		132–133 (decomp.)	140
$C_{22}H_{30}N_8O_2S_2$	Me		148–149	140
$C_{24}H_{34}N_8O_2S_2$	Et		125–127	140
$C_{24}H_{34}N_8O_4S_2$	$(CH_2)_2OH$	81	173–174	98
$C_{24}H_{36}N_8O_{10}P_2S_2$	$(CH_2)_2OPO_3H_2$	55	179–180	106, 141
$C_{24}H_{38}N_8O_{16}P_4S_2$	$(CH_2)_2[OP(O)(OH)]_2OH$		114–118 (decomp.)	106
$C_{24}H_{40}N_8O_{22}P_6S_2$	$(CH_2)_2[OP(O)(OH)]_3OH$			106, 141
$C_{26}H_{38}N_8O_2S_2$	Pr-*n*		160–161	140
$C_{26}H_{38}N_8O_2S_4$	$(CH_2)_2SMe$		165–166	93–97
$C_{26}H_{38}N_8O_4S_4$	$(CH_2)_2S(O)Me$		155.5–157	94
$C_{28}H_{38}N_8O_4S_4$	$(CH_2)_2SC(O)Me$			111, 112
$C_{28}H_{38}N_8O_6S_2$	$(CH_2)_2OAc$		119–121	105
$C_{30}H_{42}N_8O_6S_2$	$(CH_2)_2CO_2Et$		102–105	105
$C_{32}H_{46}N_8O_6S_2$	$(CH_2)_2CO_2Pr$-*n*		90–92	105
$C_{32}H_{46}N_8O_6S_2$	$(CH_2)_2CO_2Pr$-*i*		82–83	105
$C_{32}H_{42}N_8O_{10}S_2$	$(CH_2)_2CO_2(CH_2)_2CO_2H$		122–124	144
$C_{32}H_{52}N_8O_{10}P_2S_2$	$(CH_2)_2OP(OEt)_2$ ‖ O	78	113–114	145
$C_{32}H_{44}N_{12}O_8P_2S_2$	$(CH_2)_2OP(O)OH$ 			106
$C_{34}H_{50}N_8O_6S_2$	$(CH_2)_2CO_2Bu$-*i*		82–83	105
$C_{34}H_{38}N_8O_6S_4$	$(CH_2)_2CO_2$– 		142–143 (decomp.)	146
$C_{34}H_{38}N_8O_8S_2$	$(CH_2)_2CO_2$– 		129–130	146
$C_{36}H_{40}N_{10}O_6S_2$	$(CH_2)_2CO_2$– 		193	147
$C_{36}H_{54}N_8O_6S_2$	$(CH_2)_2CO_2(CH_2)_4Me$		125	105
$C_{36}H_{60}N_8O_{10}P_2S_2$	$(CH_2)_2OP(O)(OPr$-*n*$)_2$			145
$C_{38}H_{42}N_8O_6S_2$	$(CH_2)_2CO_2Ph$			148
$C_{38}H_{42}N_8O_8S_2$	$(CH_2)_2CO_2$– 		159	149
$C_{40}H_{42}N_8O_{10}S_2$	$(CH_2)_2CO_2$– 		120	150

Table 6. (continued)

Formula	R	Yield, %	m.p., °C	Ref.
$C_{40}H_{46}N_8O_6S_2$	$(CH_2)_2CO_2CH_2Ph$	43	146	105
$C_{40}H_{68}N_8O_{10}P_2S_2$	$(CH_2)_2OP(O)(Bu\text{-}n)_2$	38	92–94	145
$C_{42}H_{46}N_8O_{10}S_2$			130–135 (decomp.)	151
$C_{48}H_{52}N_8O_{10}P_2S_2$	$(CH_2)_2OP(OPh)_2$	24	153–154	145

Eight thiamine disulfides have been prepared according to the scheme:[100-104]



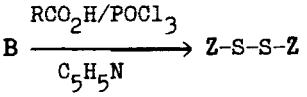


R' = Et, Pr, Bu, $CHMe_2$

R = H, Ac, Bz

Scheme 66

Thiamine disulfide, when heated with $POCl_3$ in a carboxylic acid in the presence of a tertiary amine, gives derivatives of thiamine disulfide.[105]



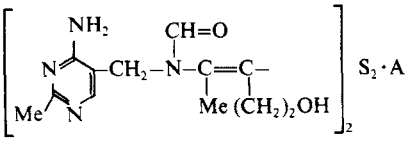
R = Me, Et, n-Pr, i-Pr, i-Bu, Bz

Scheme 67

4.2. Reactions

Thiamine disulfide, when heated in benzylamine, gives mainly the imidazolinethione **136**, the imidazole **137**, and hydrogen sulfide.[32]

Table 7. Complexes and salts of divinyl disulfides, derivatives of thiamine



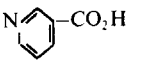
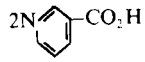
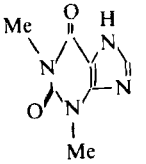
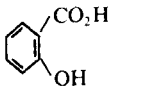
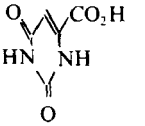
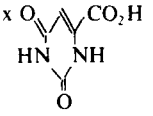
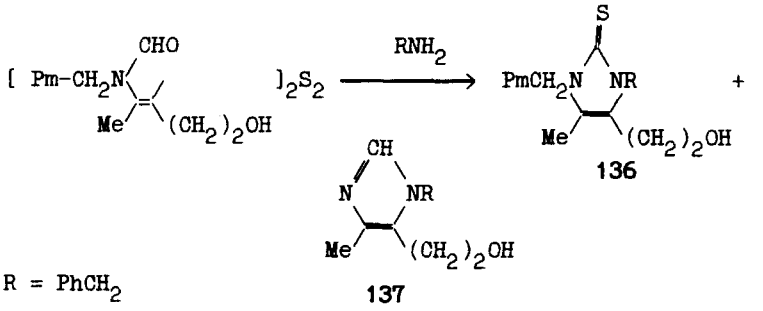
Formula	A	Yield, %	m.p., °C	Ref.
$C_{24}H_{34}N_8O_4S_2 \cdot HCl$	HCl			152
$C_{24}H_{34}N_8O_4S_2 \cdot H_3PO_4$	H_3PO_4			153
$C_{24}H_{34}N_8O_4S_2 \cdot 2HNO_3$	$2HNO_3$			154
$C_{24}H_{34}N_8O_4S_2 \cdot C_6H_5NO_2$			160–161	155
$C_{24}H_{34}N_8O_4S_2 \cdot 2C_6H_5NO_2$			158–160	156
$C_{24}H_{34}N_8O_6S_2 \cdot C_7H_8N_4O_2$ (1 : 1)		~90	154–156	113
$C_{24}H_{34}N_8O_4S_2 \cdot 2C_7H_6O_3$		100	124–126	120
$C_{24}H_{34}N_8O_4S_2 \cdot C_5H_4N_2O_4$ (1 : 1)				107, 118, 119
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{12}H_{24}O_2$	6 $C_{11}H_{23}CO_2H$	93	80–81	99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{13}H_{26}O_2$	6 $C_{12}H_{25}CO_2H$	95	75–76	99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{14}H_{28}O_2$	6 $C_{13}H_{27}CO_2H$	97	67–69	99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{15}H_{30}O_2$	6 $C_{14}H_{29}CO_2H$			99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{16}H_{32}O_2$	6 $C_{15}H_{31}CO_2H$	~95	63–65	99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{17}H_{34}O_2$	6 $C_{16}H_{33}CO_2H$	~95	59–61	99, 157
$C_{24}H_{34}N_8O_4S_2 \cdot 6C_{18}H_{36}O_2$	6 $C_{17}H_{35}CO_2H$	98	53–55	99, 157

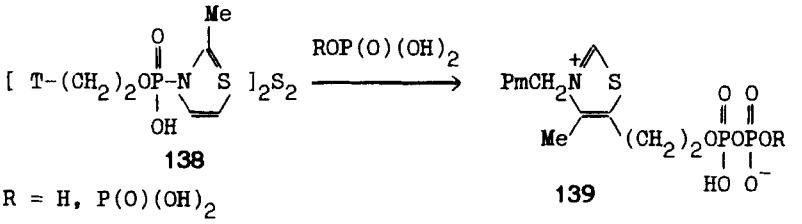
Table 7. (continued)

Formula	A	Yield, %	m.p., °C	Ref.
$C_{24}H_{34}N_8O_4S_2$ ·$xC_5H_4N_2O_4$				158



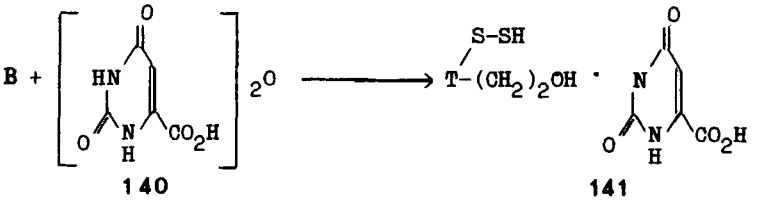
Scheme 68

The thiamine di- and triphosphates **139** have been prepared in 60 and 51% yield, respectively, by treatment of the divinyl disulfide **138** with an acid $ROP(O)(OH)_2$.[106]



Scheme 69

Reflux of orotic acid anhydride **140** with disulfide **B** in methanol (for some minutes till complete dissolution) gave the monoorotate **141**.[107]



Scheme 70

4.3. Biological Activity

Thiamine disulfide derivatives show diverse biological activity and therapeutic effects on living organisms.

Thiamine methyl-6-acetyldihydrothioacetate disulfide is a strong inhibitor of the respiration.[108]

A comparative study of the synaptoanalgesic and anesthetic effects of thiamine and various derivatives has been presented. Opening or hydrogenation of the thiazole ring do not affect, to an appreciable extent, these properties.[109]

The analgesic effect of the *O*-isobutyryl disulfide (vitaberin) on experimentally induced pain is known.[110]

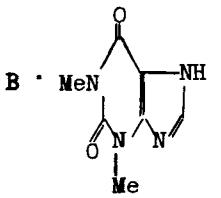
$$[\ T\text{-}(CH_2)_2OCO_2CHMe_2\ ]_2S\ 2$$

Vitaberin

Thiamine disulfides, in which the OH of the thiamine $(CH_2)_2OH$ group was replaced by NR_2, SR, S(O)R, or $S(O)_2R$, have been prepared to obtain coccidiostatic compounds.[111,112]

The complex **142** with coronary dilating and diuretic effects, useful against cardiac disease and vitamin deficiency, has been claimed.[113]

Compound **142** has an LD_{50} of 3650, 1650, and 2450 mg/kg orally, i.v., and i.p., respectively, in mice as compared to 300, 160, and 190 respectively, of theophylline.[113]



142

Vitamedin (a mixture of vitamins B_1, B_6, and B_{12}), administered to rats bearing tumors, normalized the immunity of the animals. This normalization was accelerated when thiamine monophosphate disulfide and cyanocobalamin were coadministered.[114]

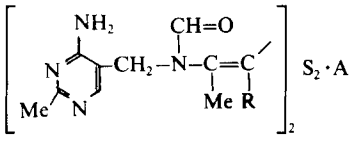
Psychoanaleptic tablets of vitaberin suppositories or parental solutions comprise 150–500 mg vitaberin dosage units.[115]

Psychotropic preparations containing vitaberin have been prepared and used in the treatment of psychic and/or behavioral disturbances due to psychostenia at dosages of 3.3–25 mg/mg/day.[116]

Vitaberin at doses higher than those commonly used in the treatment of avitaminosis B_1 shows psychoanaleptic activity.[117]

Vitaberin was also effective against juvenile asthenia and senility.[117]

Table 8. Other complexes and salts of divinyl disulfides, derivatives of thiamine



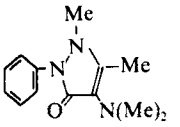
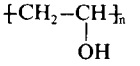
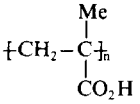
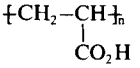
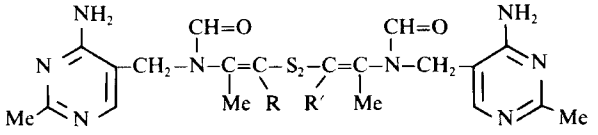
Formula	R	A	Ref.
$C_{32}H_{42}N_8O_{10}S_2 \cdot Mg$	$(CH_2)_2CO_2(CH_2)_2CO_2H$	Mg	144
$C_{38}H_{42}N_8O_6S_2 \cdot xHCl$	$(CH_2)_2CO_2Ph$	xHCl	159
$C_{38}H_{42}N_8O_6S_2 \cdot 1/2C_{12}H_{21}N_3O$	$(CH_2)_2CO_2Ph$		160
$C_{28}H_{42}N_8O_6S_2 \cdot x(C_2H_4O)_n$	$(CH_2)_2CO_2Ph$		161
$C_{38}H_{42}N_8O_6S_2 \cdot x(C_4H_6O_2)_n$	$(CH_2)_2CO_2Ph$		161
$C_{38}H_{42}N_8O_6S_2 \cdot x(C_3H_4O_2)_n$	$(CH_2)_2CO_2Ph$		161

Table 9. Nonsymmetrical divinyl disulfides, derivatives of thiamine



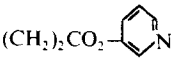
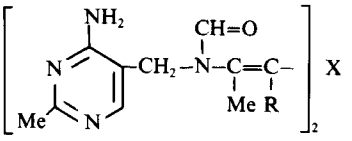
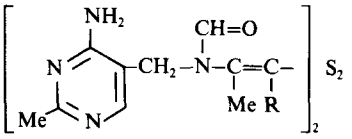
Formula	R	R′	Ref.
$C_{26}H_{38}N_8O_3S_4$	$(CH_2)_2SMe$	$(CH_2)_2S(O)Me$	94
$C_{30}H_{37}N_9O_5S_2$	$(CH_2)_2OH$		162
$C_{31}H_{38}N_8O_5S_2$	$(CH_2)_2OH$	$(CH_2)_2CO_2Ph$	20

Table 10. Oxidized divinyl disulfides, derivatives of thiamine



Formula	R	X	m.p., °C	Ref.
$C_{24}H_{34}N_8O_5S_2$	$(CH_2)_2OH$	$-\overset{\overset{O}{\|}}{S}-S-$	190–192	100
$C_{28}H_{38}N_8O_7S_2$	$(CH_2)_2OAc$	$-\overset{\overset{O}{\|}}{S}-S-$		100
$C_{32}H_{46}N_8O_7S_2$	$(CH_2)_2CO_2Pr$	$-\overset{\overset{O}{\|}}{S}-S-$	140–141	100
$C_{38}H_{42}N_8O_7S_2$	$(CH_2)_2CO_2Ph$	$-\overset{\overset{O}{\|}}{S}-S-$	153–156	104

Table 11. Symmetrical divinyl disulfides, derivatives of thiamine



R	IR (λ, cm^{-1})	UV (nm, log ε)	^1H NMR (δ, ppm)	Ref.
$(CH_2)_2OH$ carboxylic acids	3200, 1600, 1800	235, 267	0.9, 1.31 s, 1.31 s, 2.06 m, 2.90 m, 4.27 s, 6.77 s, 8.29 s	157
$(CH_2)_2-[\overset{\overset{O}{\|}}{P}(OH)]_2OH$		238		106
$(CH_2)_2CO_2-$ 	3400, 3310, 3120 (NH_2), 1715 (C=O), 682 (C–S), 810 (CH in the ring), 717, 745	240 (4.61), 272 (4.40)		146
$(CH_2)_2CO_2-$ 		240 (4.59)		146
$(CH_2)_2CO_2-$ 	1720, 1280	255 (in acid)		146
$(CH_2)_2SMe$	3400 (NH_2), 1650 (C=O)	243 (0.01 HCl)	1.77 s, 2.07 d, 2.32 s, 2.57 s, 2.5–2.8 m, 4.40 m, 6.68 broad, 7.87 s	93–97
$(CH_2)_2S(O)Me$	1050 (S=O)	233, 279 (1% $NaHCO_3$)		93–97

Thiamine disulfide **141** orotate alone or in combination with vitamin B_{12}, and/or folic acid, and/or vitamin A in various vehicles are effective in the treatment of skin diseases, mucus membrane diseases, and nail growth retardation.[118] These preparations were also effective in preventing hair loss in volunteers.[118] Thiamine disulfide monoorotate **141** (150 mg/day), given orally to human subjects for up to 4 weeks improved short-term memory.[119]

Thiamine disulfide **B** in combination with salicylic acid gave better analgesic and antiinflammatory effects than salicylic acid. Its administration (intragastric) of 150 mg/kg to rats had no significant effect on the stomach. This formulation has an oral LD_{50} of 32 g/kg in mice as compared to 1.5 g/kg of salicylic acid and is useful against rheumatoid and dermatoid diseases as well as neuritis and polyneuritis.[120]

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