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Natural polysulfides

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Contents

I.	Introduction	813
II.	Natural di- and poly-sulfides, their conversions, and biological activity	813
III.	Synthesis of natural di- and poly-sulfides and their analogues	820
IV.	Conclusion	824

Abstract. The structures of natural polysulfides of animal and plant origin are considered. Data are presented on the biological activity of compounds containing di-, tri-, tetra-, and pentasulfide groups. Schemes of total synthesis of the above-mentioned compounds and their structural analogues are discussed. The bibliography includes 156 references.

I. Introduction

Natural organosulfur compounds are abundant and structurally very diverse. The present review is dedicated to a group of natural organosulfur compounds that is scantily reviewed, *viz*., to di-, tri-, and polysulfides of plant, animal, and microbial origin. The questions pertinent to the chemistry of peptides containing a disulfide fragment are omitted from the discussion, since they have been adequately addressed in the literature (see, for example, Ref. 1).

The chemistry of simple dialkyl polysulfides of plant origin has been discussed in a number of reviews;[2–4] therefore we shall restrict our consideration to a mere mention of the discovery of a particular substance in natural objects and discuss only those questions that are related to their biological activity.

The main subjects to be considered in the review are structurally more complex low- molecular-weight di-, tri-, tetra-, and pentasulfides. They constitute a not very abundant group of natural compounds; however, in our opinion, their structures and properties are so remarkable that they deserve special discussion.

One of the major goals of this review is to attract the attention of investigators working in the field of biologically active compounds to problems of modelling of natural sulfur-containing structures and elaboration of schemes of total synthesis of the most promising representatives of this class.

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II. Natural di- and poly-sulfides, their conversions, and biological activity

1. Aliphatic di- and poly-sulfides

Aliphatic disulfides with a simple structure are the constituents of essential oils of certain plants responsible for their unpleasant odour.[5,6] For example, the essential oil obtained by steam distillation of *Ferula illiensis* Krash. roots contains 62% of *E*- and *Z*-isomeric *sec*-butyl propenyl disulfides and a small amount of *sec*-butyl methyl- and di-*sec*-butyl disulfides.[7,8] The *sec*-butyl propenyl disulfide has been also isolated from the essential oil of *Ferula asa foedida*.[6] The gum of this umbellate plant contains also methylthio derivatives of allyl sulfides: $Bu^sSSCH=CHCH_2SMe$ and $Pr^nSCH_2CH=CHSSMe$.

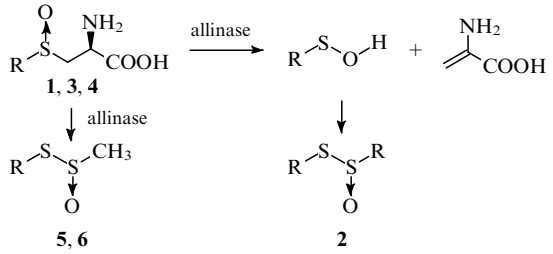
The Indian tree *Azadirachta indica* known for its potent insecticidal action produces, along with unique antifeedants of the terpenoid series (azadirachtins), also volatile polysulfides. Thus the isolation of diisopropyl di-, tri-, and tetra-sulfides as well as allylpropyl di-, tri-, and tetra-sulfides has been described.[9] It is reported that dipropyl disulfide possesses a strong larvicidal action and suppresses the reproduction of the tiger mosquito *Aedes aegypti* and the tobacco worm *Heliotis virescens*.

The curative properties of garlic and onion have been known from time immemorial. Contemporary medicine considers the therapy with preparations of garlic or onion as a prospective trend in the treatment of atherosclerosis, coronary thrombosis, asthma, and microbial infections.[10–12] Studies into the structure of the active principles of garlic and onion were undertaken in the last century. Thus steam distillation of garlic gives diallyl di-, tri-, and tetra-sulfides.[13] These compounds are formed in the course of thermal or hydrolytic treatment of native substances. The latter include alliin, [(+)-*S*-allyl-L-cysteine *S*-oxide] (**1**) first isolated from the alcoholic extract of the garlic *Allium sativum* and possessing a strong bactericidal action.[14] Intact garlic cloves contain up to 0.24% of alliin **1,** which is converted into *S*-allyl prop-2-ene thiosulfinate (allicin, **2**) by allinase.[15] This conversion passes through the stage of formation of prop-2-ene sulfenic acid, which is further self-condensed into allicin. Allicin **2** is the main component responsible for the specific odour of garlic.

Alliin **1** constitutes 83% of the total amino acid content of garlic, 13% goes to *S*-methylcysteine *S*-oxide (**3**), and 2% to the amino acid (**4**).[16] Enzymic cleavage of the amino acid **3** with allinase results in *S*-methyl methanethiosulfinate (**5**). *S*-Allylcysteine *S*-oxide **1** undergoes similar cleavage to give *S*-allyl methanethiosulfinate (**6**).[17]

The high reactivity of allicin **2** and the occurrence of other types of biochemical cleavage of alliin result in the formation of a large number of di- and tri-sulfides and their monosulfoxides

carrying different substituents. Thus a rather complex mixture of disulfides and thiosulfinates has been obtained by allinase treatment of a mixture of amino acids **1**, **3,** and **4**.



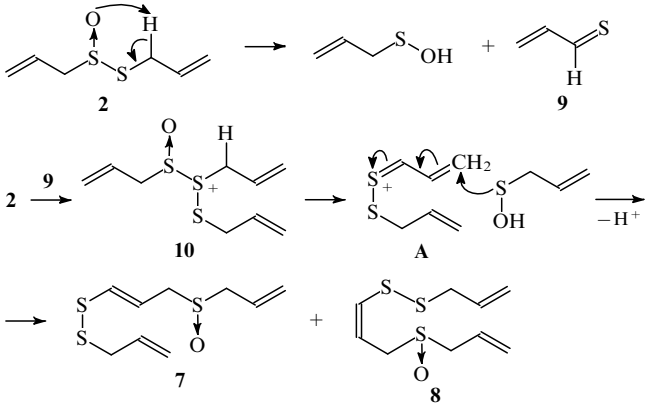
1, **3**, **4** **5**, **6** **2**

R = $CH_2CH=CH_2$ (**1**, **2**, **6**); Me (**3**, **5**); Pr^n (**4**).

Many products of steam distillation of various garlic species are identical. Thus, it has been reported that the essential oil of the South American garlic *Adenocalumma alliaceum* contains 62% of diallyl di- and diallyl tri-sulfides.[18]

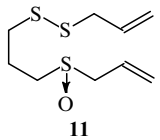
It has been established that the antithrombotic activity of garlic extracts increases upon their heating and concentration ($IC_{50} = 0.3-50$ μg ml^{-1}). Their ability to prevent coronary thrombosis and atherosclerosis and increase blood coagulation time is currently ascribed to the presence of *E*- (**7**) and *Z*-achoenes (**8**), 4,5,9-trithiadodeca-1,6,11-triene-9-oxides.[19] It is assumed that achoenes are formed from allicin according to Scheme 1.

Scheme 1



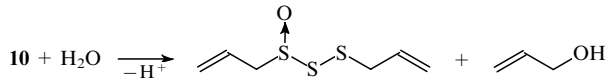
2 **9** **10** **A** **7** **8**

β-Elimination in allicin gives thioacrolein (**9**) and prop-2-enesulfenic acid. *S*-Allylthiolation of allicin results in the sulfonium ion **10,** which undergoes β-elimination to the sulfonium ion **A**. Subsequent γ-addition of prop-2-enesulfenic acid to the cation **A** gives achoenes **7** and **8**. Boiling of allicin in aqueous methanol gives 17% of a 4 : 1 mixture of achoenes **7** and **8**. One of the products of allicin conversion is dihydroachoene (**11**).[20]



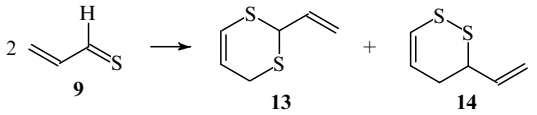
11

Another pathway of intermediate **10** conversion consists in the addition of a water molecule at the allylic double bond eventually resulting in 4,5,6-trithianona-1,8-diene-4-oxide (**12**) and allyl alcohol.



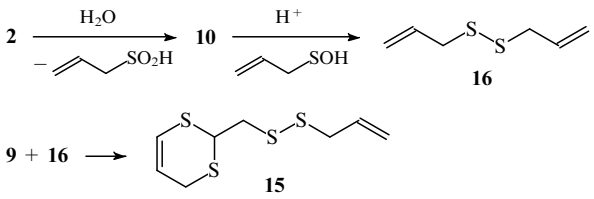
12

The involvement of intermediate thioacrolein **9** in the [4 + 2]-cyclic addition accounts for the formation of minor components of the extracts: 2-vinyl-4*H*-1,3-dithiine (**13**), 3-vinyl-3,4-dihydro-1,2-dithiine (**14**), and 2-(2,3-dithia-hex-5-enyl)-4*H*-1,3-dithiine (**15**). It is noteworthy that these dithiacyclanes have been identified among other compounds isolated from extracts and distillates of garlic.[21]



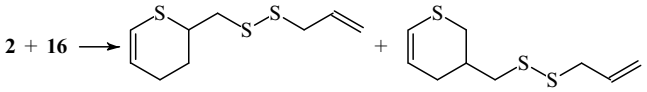
9 **13** **14**

The results of studies concerned with chemical conversions of garlic components have been discussed.[22,23] Vacuum pyrolysis of diallyl disulfide (**16**) formed from allicin **2** upon the interaction of the intermediate **10** with water gives dithiines **13** and **14** in a 4.4 : 1 ratio. Dimerisation of thioacrolein **9** in the presence of disulfide **16** results in a tetrasulfide **15**.



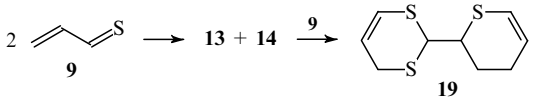
16 **15**

The thermal reaction between allicin **2** and disulfide **16** is accompanied by the formation of thio analogues of dihydropyranyl derivatives of disulfides, compounds **17** and **18**. The mechanism of this reaction is still unclear.[24]



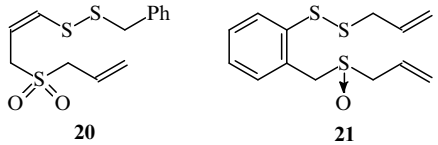
17 **18**

Of special interest are thioacrolein reactions. In addition to the aforementioned cyclodimerisation resulting in disulfides **13** and **14** (the dimerisation at 170 K gives a mixture of these dithiines in a 9 : 1 ratio in a 25% yield), the formation of the thioacrolein trimer, [2-(3,4-dihydrothiopyran-2-yl)-4*H*-1,3-dithiine (**19**)] takes place.[25]



9 **19**

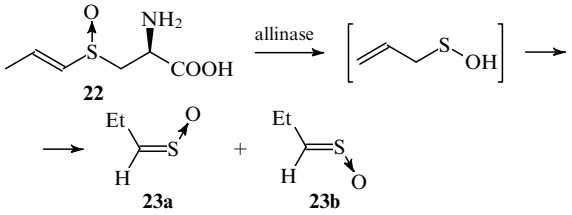
The high antithrombotic activity of achoenes **7** and **8** and dithiines **13** and **14** has stimulated the studies aimed at the synthesis of their analogues. It has been shown, in particular, that disulfides **20** and **21** possess twice as large an antithrombotic activity as *Z*-achoene (**8**).[20] This finding opens up interesting perspectives in the elaboration of valuable therapeutic drugs.



20 **21**

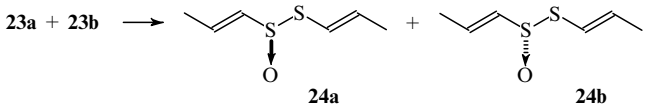
Organosulfur compounds of onion of the *Allium* genus are no less interesting. Early studies report the identification of ethyl propyl and ethyl isopropyl disulfides, butyl propyl and butyl isopropyl disulfides, diallyl disulfide, diallyl trisulfide, methyl propyl and allyl methyl tetrasulfides, allyl propyl tetrasulfide, dimethyl pentasulfide, and methyl propyl pentasulfide as the components of the onion *Allium cepa*.[26,27] Wild varieties of onions of the *Allium* genus contain dipropyl disulfide and allyl methyl trisulfide.[28,29] The essential oil of the onion *Allium cepa* contains no less than 100 compounds of which 39 organosulfur compounds have been reliably identified.[30] Methyl propyl disulfide, dipropyl disulfide, (*Z*)- and (*E*)-allyl propyl disulfide, dipropyl trisulfide, (*Z*)- and (*E*)-allyl methyl trisulfides, (*Z*)- and (*E*)-allyl propyl trisulfides, methyl propyl tetrasulfide, dipropyl tetrasulfide, (*Z*)-

and (*E*)-allyl propyl tetrasulfides, dimethyl pentasulfide, and methyl propyl pentasulfide are the major components. The ratio of allyl, methyl, and *n*-propyl residues is 85 : 13 : 2; diallyl disulfide makes up 30% – 50% of the total mixture.[29] In addition to the polysulfides mentioned above, steam-distillation products have been found to contain cyclic and acyclic vinyl thiosulfinates. [(+)-*S*-(*E*)-Propenyl]-L-cysteine *S*-oxide] (**22**), the amino acid isomeric to alliin, is the precursor of organosulfur components. Its enzymic cleavage gives stereoisomeric propanethioaldehyde *S*-oxides (**23a**,**b**), of which the former predominates.



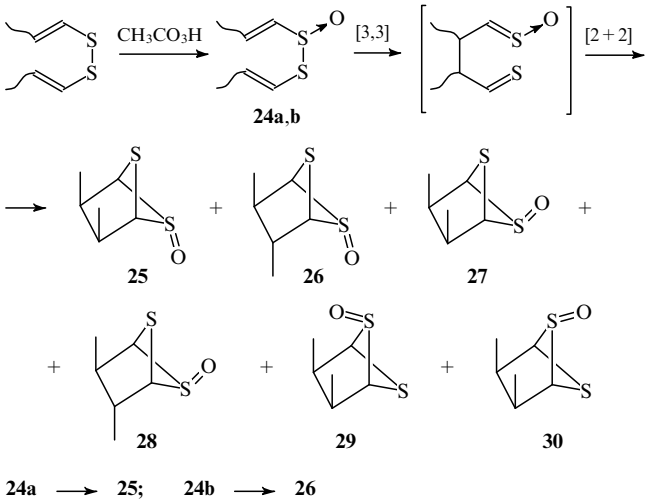
22 **23a** **23b**

Both compounds are responsible for lacrymatory properties of the onion. Their self-condensation results in the formation of *S*-*E*-propenyl *E*-prop-1-enethiosulfinates (**24a**,**b**). The condensation involves the intermediate prop-1-enesulfenic acid and methane- and propanesulfenic acids formed upon enzymic cleavage. Compounds **23a**,**b** and **24a**,**b** are the main carriers of the onion odour.[30]



24a **24b**

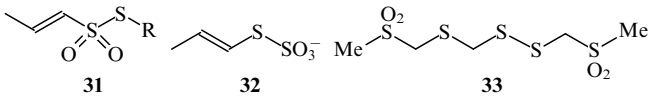
Zwiebelans — 1α,2α,3α,4α,5β- and 1α,2α,3β,4α,5β-2,3-dimethyl-5,6-dithiabicyclo[2.1.1]hexane-5-oxides (**25**, **26**) — are also the onion flavourants. Their formation is accounted for by a transformation of dipropenyl disulfide monosulfoxide, which involves the Cope rearrangement as the first step followed by [2 + 2]-cycloaddition. When a mixture of stereoisomeric dipropenyl disulfides had been used, the reaction gave six dithiabicyclanes (**25** – **30**).[31] The synthesis of dithiabicyclanes in plants is stereospecific: *S*-(*E*)-prop-1-enyl (*E*)-prop-1-enylthiosulfinate (**24a**) gives zwiebelan **25**, whereas the *Z*-isomer **24b** gives zwiebelan **26**.[32]



24a,**b** **25** **26** **27** **28** **29** **30**

24a ⟶ **25**; **24b** ⟶ **26**

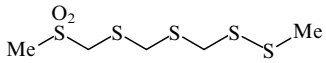
The high biological activity of dithiabicyclo[2.1.1]hexane derivatives can be inferred from the fact that a mixture of zwiebelans **25** and **26** isolated from *Allium cepa* extracts inhibits by 65% – 90% the biosynthesis of leukotriene TXB_2 in human cells when used in concentrations of 0.1 – 1.0 mg ml^{-1} (see Ref. 31). The identification of thiolsulfonates **31** and Bunte salts **32** in onion extracts has been reported.[31]



31 **32** **33**

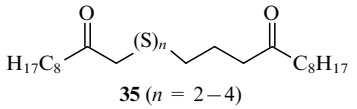
The medicinal plant *Dysoxylum richii* growing in the Fiji Islands is used by the local population as a tea additive and a means of prophylaxis against diseases caused by pathogenic microorganisms. The active principle of this plant is dysoxysulfone, 2,4,5,7,9-pentathiadecane-2,2,9,9-tetraoxide **33,** which is a potent inhibitor of the proliferation of *Staphylococcus aureus, Bacillus subtilis,* and *Candida albicans*. The minimum inhibiting concentrations (MIC) of **33** for these microorganisms are 100, 20 and 10 μg plate^{-1}, respectively.[33] In addition, this compound manifests high antitumour activity against human ovarian carcinoma cells (IC_{50} = 5 μg ml^{-1}; the corresponding value for large intestinal adenocarcinoma is 7.4 μg ml^{-1}).[32] This plant is the second representative of the *Meliaceae* family after *Azadirachta indica* that produces sulfur-containing metabolites.

High antitumour activity has also been observed for 2,3,5,7,9-pentathiadecane-9,9-dioxide **34** isolated from the 'Shitake' fungus *Lentinus edodes* (IC_{50} for murine leukemia cells is 0.62 μg ml^{-1}).[34]

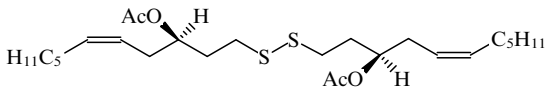


34

The Hawaian sea algae *Dictyopteris plagiogramma* are rich in saturated and unsaturated linear C_{11} hydrocarbons. The isolation of oxo-oligosulfides **35** and diacetoxydisulfide **36,** which can be considered as precursors of undeca-1,3,5-trienes, has been described.[35 – 37]



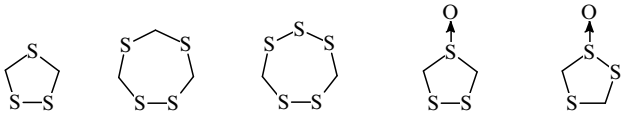
35 (*n* = 2 – 4)



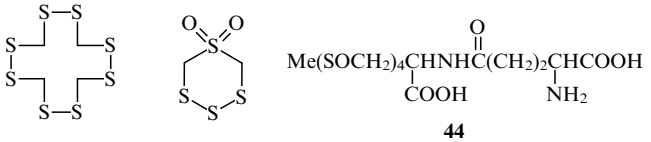
36

2. Saturated cyclic di- and poly-sulfides

Cyclic oligo- and poly-sulfides **37** – **43** have been isolated and identified as carriers of antibacterial activity in extracts of the red algae *Chondria californica*.[38] These thiacyclanes can be regarded as the products of condensation of formaldehyde with hydrogen sulfide. The highest antibiotic activity in this series of compounds is manifested by 1,2,3,5-tetrathiane-5,5-dioxide (**43**), which inhibits the growth of *Vibrio anguilarum, Proteus mirabilis, Salmonella typhimurium,* and *E.coli* in a concentration of 10 μg ml^{-1}. Sulfoxides **40** and **41,** which can be obtained from 1,2,4-trithiolane **37,** also possess antibiotic activity. 1,2,3,5,6-Pentathiepane (**39**) is identical to the so-called lenthionine produced by the fungus *Lentinus edodes*. Lenthionine is biogenetically related to lenthinic acid (**44**).[39] Extracts of other *Chondria* species are devoid of antimicrobial activity and do not contain cyclic polysulfides.



37 **38** **39** **40** **41**

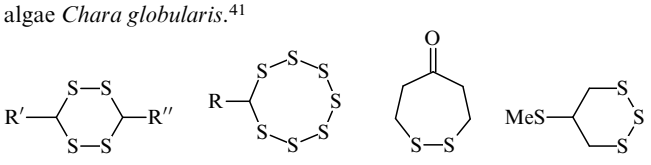


42 **43**

44

Cyclic polysulfides of the type 1,2,4-trithiolane (**37**), 1,2,3,5,6-pentathiepane (**39**), 1,2,4,5-tetrathiane (**45**), and 1,2,3,4,5,6,7-heptathiocane (**46**) have been isolated from the cultural fluid produced by *Thermococcus* cells.[40] Studies of biological activity of these compounds have revealed that the highest fungicidal activity is exerted by pentathiepane **39** (7.8 μg ml^{-1} with respect to *Microsporum canis*). The *in vitro* antihelminthic activity against *Caenorhabditis elegans* has been established for thiolane **37**. It has been found that alkyl-substituted polysulfides **46** are unstable and decompose to yield sulfur and disubstituted cyclic polysulfides.

Saturated six- and seven-membered di- and tri-sulfides are rather rare. So far only one seven-membered cyclic disulfide **47** isolated from the alga *Dictyopteris plagiogramma* is known.[35] 5-Methylthio-1,2,3-trithiane (**48**) has been isolated from the green algae *Chara globularis*.[41]



45 **46** **47** **48**

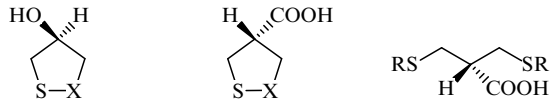
3. 1,2-Dithiolanes and their derivatives

Of great biological importance are functionally substituted derivatives of 1,2-dithiolane isolated from animal and plant objects.

Thus the diastereoisomeric 1,2-dithiolane-1-oxides brugierol (**49a**) and isobrugierol (**49b**), which control plant growth have been isolated from the methanolic extract of the bark of *Brugiera conjugata*.[42, 43]

A potent plant growth inhibitor, whose action is similar to that of abscisic acid, is asparagusic (1,2-dithiolane-4-carboxylic) acid (**50**) isolated from young sprouts of asparagus (*Asparagus officinalis* L.).[44]

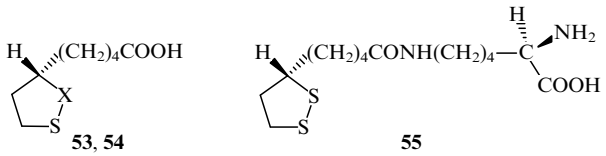
Asparagusic acid sulfoxides (**51a**,**b**) obtained by extraction of asparagus sprouts with methanol manifest high growth-regulating activity.[45] It is noteworthy that dihydroasparagusic acid (**52a**) and its diacetate (**52b**) have also been isolated from the asparagus plant. This suggests that asparagusic acid plays the key role in the biochemically important process of acetyl group transport mediated by acetyl-CoA.



49a,**b** **50**, **51a**,**b** **52a**,**b**

49a: X = S⇢O; **49b**: X = S→O; **50**: X = S; **51a**: X = S⇢O; **51b**: X = S→O; **52a**: R = H; **52b**: R = Ac.

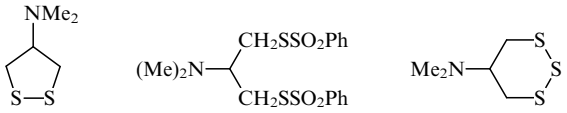
This group of disulfides includes lipoic acid (**53**) and its sulfoxide, β-lipoic acid (**54**), present in both animal and plant organisms. Lipoic acid plays the role of an acetyl group transfer factor and a factor promoting the growth of bacteria and *Protozoa*. In the form of protein-bound ε-lipoyllysine (**55**), lipoic acid and its reduced form, dihydrolipoic acid, are the coenzymes for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase responsible for oxidative decarboxylation of α-keto acids with the transfer of the acetyl group to coenzyme A. The participation of lipoic acid in thiol-disulfide conversions of proteins, oxidative phosphorylation, and arachidonic acid conversion into prostaglandin H has also been established.[1, 46] Lipoic acid participates in the primary step of the quantum of light conversion in photosynthesis.[47] In the form of vitamin N, lipoic acid is used in the treatment of liver disorders, diabetes, atherosclerosis and other diseases resulting from disturbances in lipid metabolism.



53, **54** **55**

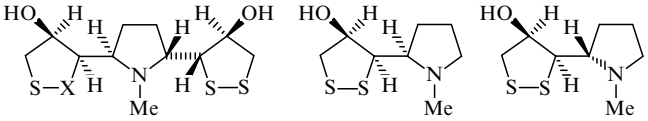
X = S (**53**), SO (**54**).

4-Dimethylamino-1,2-dithiolane — nereistoxin (**56**) — isolated from the sea worm *Lumbriconereis heteropoda* possesses unique insecticidal activity.[48, 49] This simple molecule has served as a model in the synthesis of highly effective insecticides.[50] For example, the compound bensultap (**57**), which exhibits high selectivity against Coleoptera,[51] has been recommended for suppressing the reproduction of the Colorado potato beetle without any detriment to beneficial insects, bees, and fish. The practical application of 5-dimethylamino-1,2,3-trithiane (**58**) as insecticide has been reported.[49, 52]

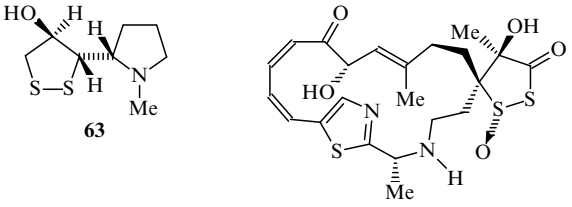


56 **57** **58**

The bark of the Brazilian tree *Cassipourea guianensis* contains a group of alkaloids of the 1,2-dithiole type. The main component of the extract, gerardin (**59**), is a potent fungistatic agent. Quinesins A, B, C, and G (compounds **60**–**63**, respectively) possess high insecticidal activity.[53–55] The antibiotic leunamycin (**64**) produced by *Streptomyces sp*. and possessing strong antitumor activity [56, 57] is also a 1,2-dithiole derivative.



59: X = S; **62**: X = SO. **60** **61**



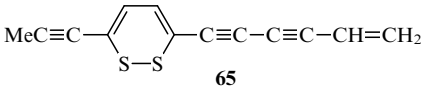
63 **64**

4. 1,2-Dithiins

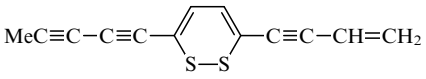
Increasing attention is presently focussed on a novel class of sulfur-containing heterocyclic compounds, 1,2-dithia-cyclohexa-3,5-dienes, in connection with their unusual structure and a broad spectrum of biological activity. Thus very promising candidates for antiviral and antibacterial agents are acetylenic derivatives of this heterocycle. Red coloured thiarubrins A (**65**) and B (**66**) are produced by many plants used as curative agents in the folk medicine of some African countries. For example, leaves of the African plant *Aspilia africana,* which contain thiarubrins A and B, are used for the treatment of abdominal infections. It has been noted also that these leaves are chewed by chimpanzees.[58] 3-(Hex-5-en-1,3-diynyl)-6-(1-propynyl)-1,2-dithiin **65** possesses antiviral, fungicidal, and antibacterial activities (when used at a concentration of 10^{-7} mg ml^{-1}) and inhibits the growth of *Candida albicans* at the level of the drug funizen.[59]

Other sources of thiarubrins are: *Aspilia mossambicensis, A. plurisetta,*[60] *Ambrosia artemisiifolia*,[61] *Pegolettia senegalensis*,[62] *Wedelia hookeriana*,[63] *Schkhuria multiflora*,[64] *S. senecioides*,[65] *Chaenactis douglasii, Eriophyllum lanatum*[66] and *Eriophyllum caespitosum*.[65, 67]

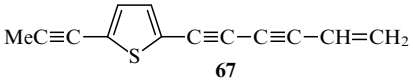
It is noteworthy that thiarubrins are present in the plants together with the corresponding thiophenes (**67**, **68**).[68]



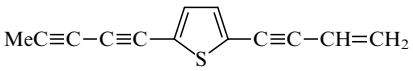
65



66

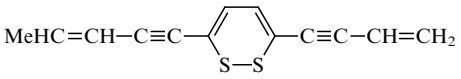


67

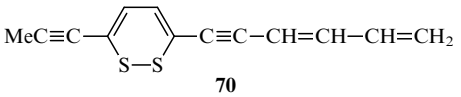


68

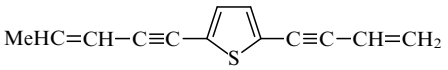
Some plants of the *Compositae* family produce dihydrothiarubrins (**69**, **70**) and thiophenes genetically linked to them (**71**, **72**). For instance, dithiin **69** has been isolated from *Picradeniopsis woodhousei*,[69] *Lasthenia*[70], and *Ogedaea boliviana*,[71] whereas 2,5-disubstituted thiophene **72** is present in the plant *Melampodium divaricatum*.[72]



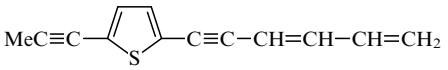
69



70



71



72

3-Vinyl-3,4-dihydro-1,2-dithiin (**14**) isolated from garlic has been also identified among compounds that determine the odour of cooked asparagus.[73]

The chemistry of 1,2-dithiin derivatives has been reviewed.[74]

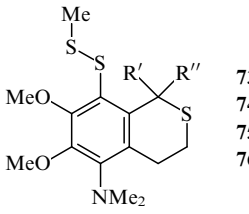
5. Di- and poly-sulfides carrying aromatic or heteroaromatic substituents

Di- and poly-sulfides having in their structure a functionalised aromatic or heterocyclic (imidazoline, thiazole) fragment possess valuable biological activity. Compounds, in which these fragments are either linked together with S–S bonds, or contain a cyclic polysulfide fragment or a terminal methyldithio substituent, have been isolated.

Thus polycarpamines A–D (compounds **73**–**76**) isolated from the ascidia *Polycarpa aurata* manifest high *in vitro* inhibitory activity against *Candida albicans* and *Saccharomyces cerevisiae*.[75] The sponges *Psammaplysilla purpurea* contain psammoplins A (**77**) and D (**78**) suppressing the growth of the gram-positive bacteria *Staphylococcus aureus* and *Trychophyton mentagrophytes*.[76]

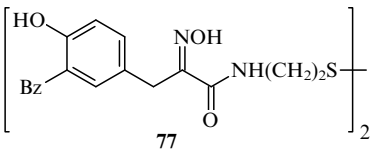
Amino acids of unusual structure **79** have been isolated from the starfish *Astropecten latespinasus*. They exhibit cytotoxic activity against KB-cells ($IC_{50} = 3 \times 10^{-6}$ mg ml^{-1}).[77]

The disulfide polycarpine (**80**) has been recently isolated from a methanolic extract of the ascidian *Polycarpa aurata*. At a concentration of 0.19 μmol litre^{-1} it inhibits inosine monophosphate dehydrogenase. The fact that the inhibition can be eliminated by excess of dithiothreitol suggests that alkaloid **80** reacts with sulfhydryl groups of the enzyme.[78]

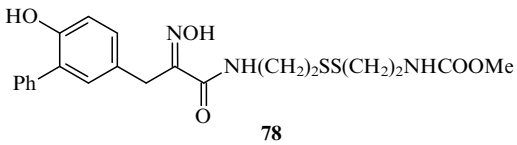


73: R′ = H, R″ = OMe;
74: R′, R″ = O;
75: R′, R″ = S;
76: R′ = OMe, R″ = COOMe.

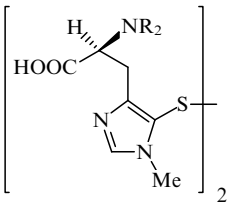
73–76



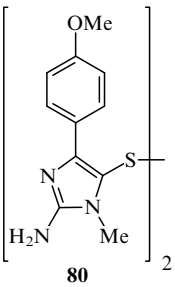
77



78



79: R = H, Me.



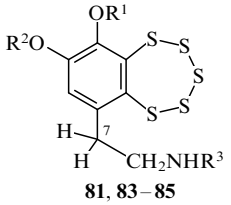
80

The tunicate *Lissoclinum perforatum* residing in North England contains 6,7-benzo-1,2,3,4,5-pentathiepanes with an annelated aromatic fragment: lissoclinotoxins A (**81**) and B (**82**) and isolissoclinotoxin A (**83**).[79, 80] Lissoclinotoxin A **81** is a potent antimicrobial agent. Its activity against *Staphylococcus aureus, Streptococcus faecalis,* and *Citrobacter sp.* (MIC = 0.08–0.6 μg kg^{-1}) markedly exceeds that of the cephalosporine antibiotic cephotaxim. It also manifests sufficiently high activity against *E.coli, Salmonella sp., Proteus sp.,* and *Pseudomonas aeruginosa*. Lissoclinotoxins A and B, especially compound **82** suppress ichthyopathogenic strains of *Aeromonas salmonicida* 643 and *Vibrio anguillarum* 5536.

Lissoclinotoxin A demonstrates a rather high activity against the malaria pathogen *Plasmodium falciparum,* which is resistant to antimalarial drugs, such as mefloquinine, galofantrin, and chloroquine. It exhibits the remarkable capacity to inhibit the growth of leukemia L 1210 cells when used at a concentration of 1 μg ml^{-1}. Lissoclinotoxin A manifests cytotoxic properties suppressing cell division in the sea urchin test.[80]

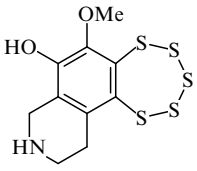
The antitumor activity of varacin exceeds 100-fold that of 5-fluorouracyl. Lissoclinotoxins C (**87**) and D (**88**), genetically related to lissoclinotoxin A, have been isolated from the tropical ascidia *Lissoclinum vareau*.[81] These molecules are not diastereotopic. Lissoclinotoxin D, a dimeric derivative of lissoclinotoxin C, exerts fungicidal activity against *Candida albicans* at the same level as lissoclinotoxin A, whereas compound **88** is inactive.

The tropical ascidia *Lissoclinum vareau* contains varacin (**84**) possessing the fungicidal activity against *Candida albicans* and inhibiting the growth of human carcinoma HCT-116 cells (IC_{90} = 0.05 μg ml^{-1}).[81]

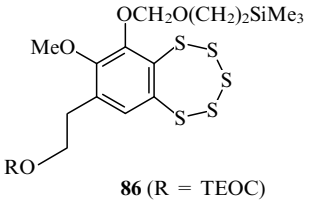


81: R^1 = Me, R^2 = R^3 = H;
83: R^1 = R^3 = H, R^2 = Me;
84: R^1 = R^2 = Me, R^3 = H;
85: R^1 = R^2 = Me,
R^3 = $COO(CH_2)_2SiMe_3$ (TEOC).

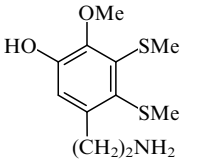
81, **83–85**



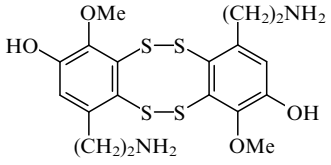
82



86 (R = TEOC)



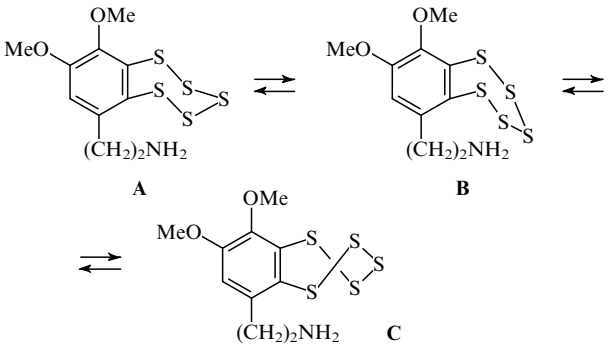
87



88

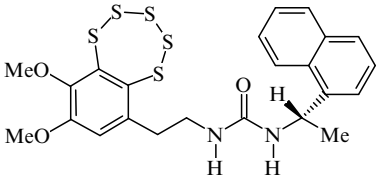
Lissoclinotoxins **81**–**83** and varacin **84** are the first presently known natural benzopentathiepine derivatives. Analysis of ^{1}H NMR spectra of compounds **81**, **84**, and their derivatives allowed one to conclude about the chirality of these molecules. Thus diastereotopicity of C(7)-methylene group protons has been observed in the spectrum of *N*-trimethylsilylethoxycarbonylvaracin (*N*-TEOC-varacin) (**85**)[82] and lissoclinotoxin A (**81**).[83] In compound **86,** the protons of the trimethylsilylethoxymethyl group are diastereotopic.

Thus, the interconversion of the benzopentathiepine system does not take place at room temperature. The inversion barrier in the lissoclinotoxin A molecule is 29 kcal mol^{-1}.[83] Calculations performed by the molecular mechanics method suggest that the chair (**A**) conformation for compound **84** is preferential as being energetically the most favourable. The second stable conformation, the energy of which is 8.7 kcal mol^{-1} higher, is the 'twist' conformation **C**. The transition from the conformation **A** to the conformation **C** proceeds *via* the conformation **B**, the energy of which is higher than that of the conformation **A** by 34 kcal mol^{-1}.

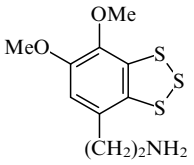


A **B** **C**

The ^{1}H NMR spectrum of a varacin derivative **89** contains double signals of the proton of the benzene ring and of both methoxy groups. This suggests the presence of two stereoisomers. A sample enriched with one isomer by 75% could be obtained by crystallisation.



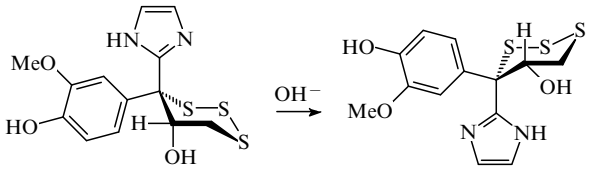
89



90

A benzotrithiane derivative **90** with fungicidal and antimicrobial activities against gram-positive and gram-negative bacteria (MIC = 0.1–0.6 μg ml^{-1}) and the fungi *Candida albicans* (40 μg ml^{-1}) and *Trichophyton mentagrophytes* (20 μg ml^{-1}) has been isolated from the tropical ascidian *Lissoclinum perforatum*.[79]

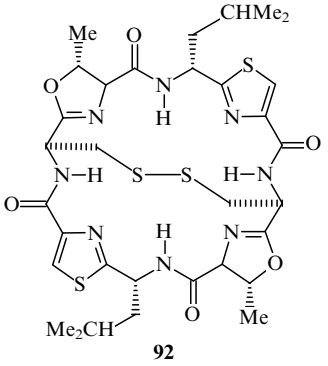
The ascidia *Aplidium pliciferum* contains a trisulfide **91a** possessing antimicrobial, antitumour, and cytotoxic activities.[84] In alkaline media, the sulfur-containing ring is inverted to give a more stable diastereoisomer **91b** with an opposite configuration of the chiral carbon atom. Using NMR and molecular mechanics methods, it has been established that the trithiane ring in the epimer **91b** has a chair conformation in which the hydroxyl group occupies the equatorial position, whereas the imidazole ring is in the axial position. Based on the analysis of the NMR spectrum of the natural isomer **91a**, the chair conformation with the axial position of the hydroxyl group has been ascribed to the trithiane ring. Molecular modelling offers an alternative interpretation which entails rapid interconversion of two possible chair configurations. Both stereoisomers possess high biological activity: IC_{50} values for their cytotoxic action against leukemia P 388 cells are 13 and 12 μg ml^{-1}, respectively.[84]



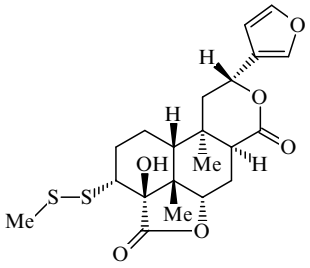
91a **91b**

An unusual cyclopeptide ulthiacyclamide (**92**) the molecule of which is built of two unusual amino acids is produced by the ascidian *Lissoclinum patella*. It is reported that compound **92** possesses strong cytotoxic activity and inhibits the growth of leukemia L1210 (at a concentration of 0.35 μg ml^{-1}) and human carcinoma CEM cells (at a concentration of 0.012 μg ml^{-1}).[85–87]

The terpenoid disulfide menispermacide (**93**) has been isolated from the plant *Tinospora malabarica* of the *Menispermaceae* family.[88] This compound is the first representative of sulfur-containing terpenoids of the clerodane series.



92



93

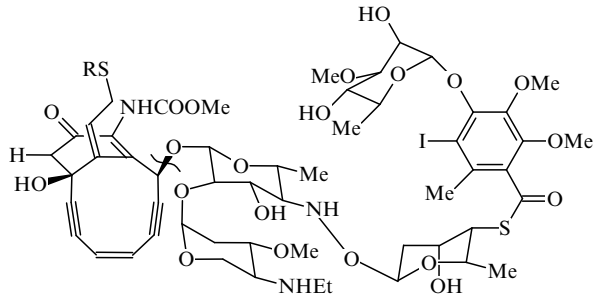
6. Antibiotics containing an enediyne fragment

Considerable interest in the past decade has been addressed to novel antibiotics, the aglycone fragment in which is an oxotrisulfide having the skeleton of a bicyclo[7.3.1]trideca-5-ene-3,7-diyne.

Thus calichemycin γ_1 (**94**) produced by the culture of *Micromonospora echinospora* possesses extraordinary antitumour activity, which exceeds 4000-fold that of adriamycin, one of the best modern cancerostatic agents.[89–95]

The antitumour and cytotoxic activities of calichemycin γ_1 and its synthetic analogue, calichemycin θ_1 (**95**)[95] in which the trisulfide fragment had been replaced by the etylthio group, have been studied with respect to a vast variety of cells beginning with the relatively stable melanoma SK MEL 28 cells (IC_{50} = 1.6×10^{-9} M) and ending up with highly sensitive leukemia MOLT-4 cells ($IC_{50} = 10^{-12}$ M).

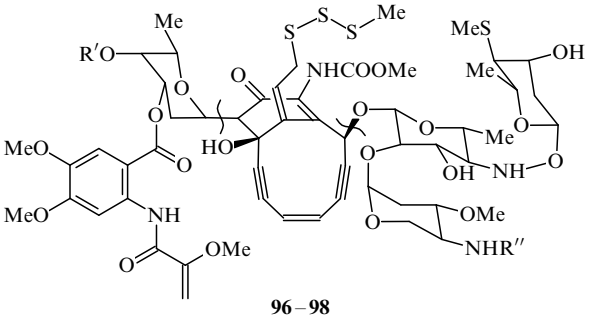
Esperamycins A_1, A_2 and A_{1b} (compounds **96**–**98**, respectively) also appear to be potent cancerostatic agents.[96–98] These strikingly remarkable molecules are unique in all the elements of



94, **95**

R = SSMe (**94**), Ac (**95**).

their structure. Thus the structure of the carbohydrate skeleton and of the aglycone of the antibiotics has no precedents in the chemistry of natural compounds. Carbohydrate fragments involve rare thio- and amino sugars linked through a unique, hydroxylamine bond. The structures of the polysubstituted benzoic acids deserve individual mention.

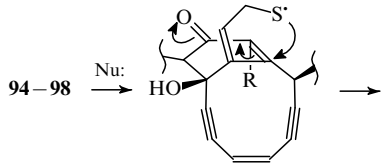


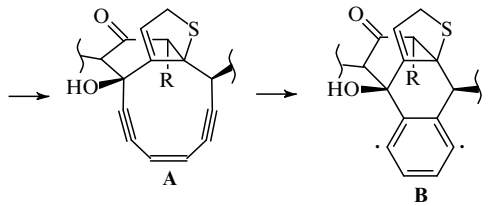
96–**98**

96: R′ = H, R″ = Pr^{i}; **97**: R′ = Ac, R″ = Bu^{t}; **98**: R′ = H, R″ = Et.

The mechanism of the anticarcinogenic effect of enediyne antibiotics entails active involvement of the trisulfide fragment. At the first stage, the enediyne system forms associates with double-stranded DNA; the complex formation affects predominantly the DNA region enriched with pyrimidine bases. Using ^{1}H NMR technique, the formation of a 1 : 1 complex with a duplex containing the A-C-C-T fragment, and of a 1 : 1 complex with the T-T-T-T fragment has been established. It is reasoned that the coordination with the pyrimidine-containing fragments is conformationally more favourable than that with the purine fragments.[99]

An important role in the binding to DNA is ascribed to the side chain of enediyne antibiotics **94**–**98**. The analysis of six models of calichemycin complex formation has led to a conclusion that the model that involves the binding of rhamnose, thiobenzoic acid, and the thio sugar to the DNA region 5′-T-C-C-T/3′-A-G-G-A is more preferable.[100, 101] Cleavage of the trisulfide fragment is crucial for the stage of conjugated addition of the thiol residue according to the anti-Bredt rule. Bioreduction to the dihydrothiophene intermediate **A** initiates the key Bergman cyclisation, eventually resulting in the conversion of enediyne into diyl (**A** → **B**). Diyl **B** is responsible for DNA cleavage that begins with hydrogen detachment from the 2-deoxyribose residue.[102, 103] The mechanism of activation of calichemycin θ_1 (**95**) is different in that an oxygen-, sulfur-, or nitrogen-containing nucleophile is used as an activator, whereas enediynes **94** and **96**–**98** are activated by thiols.[95] The problem of complex formation of calichemycin γ_1 is also discussed in a paper by Mah *et al.*,[104] which also gives a detailed list of references.





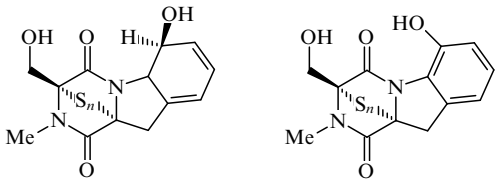
A **B**

R = NHCOOMe.

7. Sulfur-containing piperazinediones

Let us now dwell on the characteristics of fungal metabolites that have a polythiapiperazinedione fragment in their structure. The chemistry and toxicology of these compounds and the literature coverage of up to 1980 have been reviewed.[105, 106]

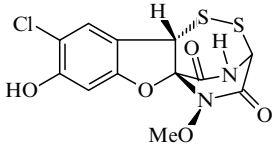
Glyotoxin (**99**) produced by *Aspergillus fumigatus, Gliocladium fimbriatum,* and *Pennicillium terlikowski* is highly toxic against homoiothermal organisms.[107–109] Dehydroglyotoxin (**100**) and the corresponding trisulfide (**101**) have been isolated from the metabolites of the fungus *Pithomyces chartarum*.[110, 111] The tetrasulfide (**102**) termed glyotoxin G has been identified as a minor metabolite of *Aspergillus fumigatus*.[109, 112]



99, **102** **100**, **101**

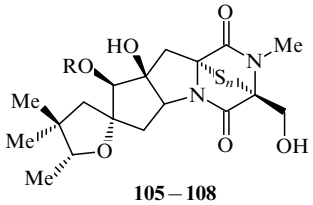
n = 2 (**99**, **100**), 3 (**101**), 4 (**102**).

The fungus *Aspergillus tamari* produces a chlorophenolic metabolite aspirochlorine (**103**).[113, 114] Aspirochlorine (**103**) is highly active *in vitro* against gram-positive bacteria and fungi (IC_{50} = 0.1–50 mg kg^{-1}); however, in contrast with the epidithiapiperazine-2,5-diones (**99**–**102**) described above, it exhibits only slight fungicidal and antiviral activities.[115] The above-mentioned differences in biological activity can be due to differences in the strain of bicyclo[2.2.2] systems in **99** and **100** and bicyclo[3.2.2] systems in **103**. Like glyotoxins **99**–**102**, aspirochlorine is a strong immunosuppressor and inhibits phagocytosis.[116]



103

A phytopathogen *Phoma lingam* affecting rape and cabbage produces several toxins. One of them, phomalirazine (**104**), is produced exclusively by this fungus. The other two compounds, sirodesmins PL (**105**) and H (**106**), are also metabolites of the fungus *Sirodesmium diversum*.[117, 118] The latter also produces sirodesmins B (**107**) and C (**108**).

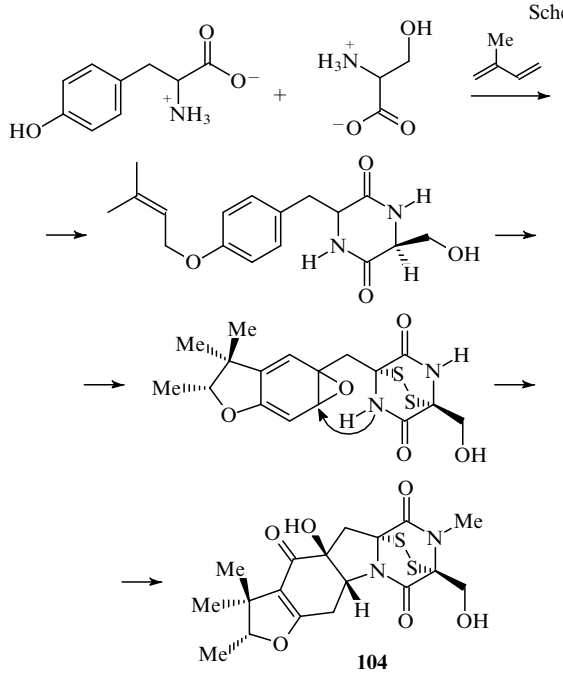


105: *n* = 2, R = Ac;
106: *n* = 2, R = H;
107: *n* = 4, R = Ac;
108: *n* = 3, R = Ac.

105–**108**

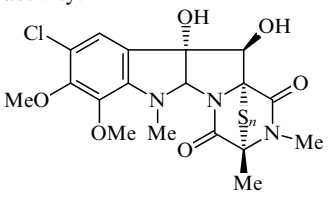
Sirodesmins possess antiviral activity against *Vaccinia, Herpes,* and Newcastle disease viruses.[119] Phomalirazine is the precursor of sirodesmins. Its biosynthesis begins with tyrosine and serine and involves isoprene (Scheme 2).[118]

Scheme 2



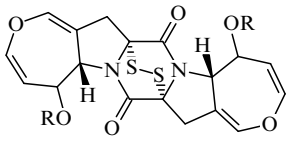
104

Sporidesmins A, E, and G (**109**–**111**) isolated from the culture of the fungus *Phithomyces chartarum* possess marked antibiotic activity.[108, 111, 120]



109–**111**

n = 2 (**109**), 3 (**110**), 4 (**111**).



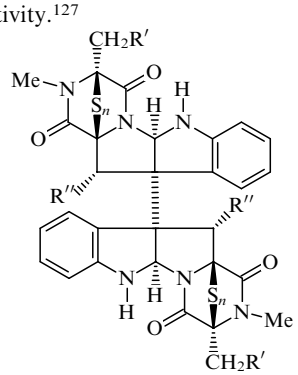
112, **113**

R = H (**112**), Ac (**113**).

Metabolites of the fungus *Arachniotus aureus* have been found to contain dithiapiperazinedione aranotine (**112**) and its diacetate **113**, which exhibit *in vitro* and *in vivo* antiviral effects.[121, 122] The latter is also produced by *Aspergillus*.[123]

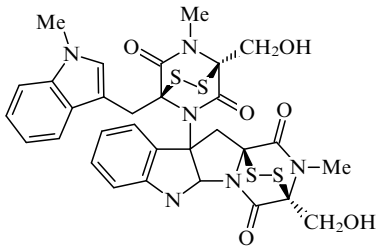
Chetocine (**114**)[108] and chetomine (**115**) are metabolites of the fungi *Chaetomium minitum* and *Ch. cochliodes*.[124] The latter compound is highly toxic against homoiothermal organisms. High antibacterial activity has been established for chetocine **114** (MIC for *Staphylococcus aureus* is 0.01–0.001 mg ml^{-1}), and its cytotoxicity index (IC_{50}) with respect to P-815 tumour cells is 0.038 mg litre^{-1}.

Fungi *Verticillium* produce the antibiotics verticillins A–C (**116**–**118**), which suppress gram-positive and gram-negative bacteria and inhibit the growth of some other fungi and cancer cells[125,126] (the cytotoxic effect, ED_{50}, of compounds **116** and **117** with respect to HeLa cells is 0.2 μg ml^{-1}). It is interesting to note that polythiapiperazinediones **114**–**118** are devoid of antiviral activity.[127]



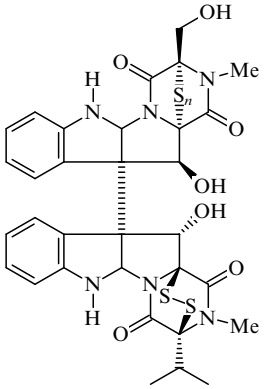
114: R′ = OH, R″ = H, n = 2;
116: R′ = H, R″ = OH, n = 2;
117: R′ = R″ = OH, n = 4;
118: R′ = R″ = OH, n = 3.

114, **116**–**118**



115

The structure of leptosines A–C (**119**–**121**), the secondary metabolites of the fungi *Leptosphaeria sp*. isolated from the sea alga *Sargassum forfile* has been recently established. Their high antitumour activity has been reported.[128, 129]



119, **120**, **121**

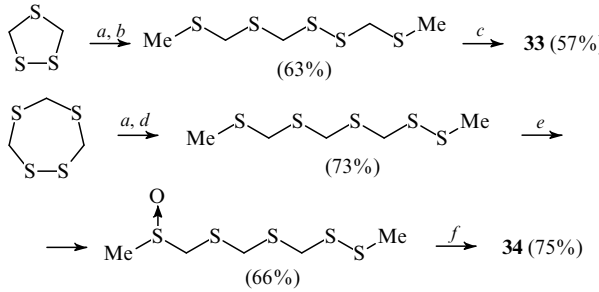
n = 2 (**119**), 3 (**120**), 4 (**121**).

III. Synthesis of natural di- and poly-sulfides and their analogues

As can be seen from the presented data, naturally occurring polysulfides present special interest by virtue of their unusual stuctures and remarkable physiological activity. The latter fact has stimulated studies aimed at total synthesis of these compounds and their structural analogues.

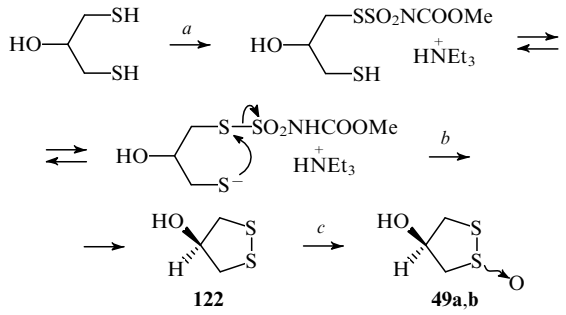
Syntheses of the biologically active linear polysulfides, *viz*., 2,4,5,7,9-pentathiadecane-2,2,9,9-tetraoxide (**33**), 2,3,5,7,9-pentathiadecane-9,9-dioxide (**34**), and 2,4,5,7-tetrathiaoctane-2,2-dioxide isolated from the plant *Tulbaghia violacea*[130] have been carried out starting from the corresponding polythiacyclanes. The key stage in these syntheses is the nucleophilic ring-opening of 1,2,4-trithiolane (**37**), 1,2,4,6-tetrathiepane (**38**), and 2,4,5,7-tetrathiaoctane with MeLi, trapping of thiolate ions formed by electrophiles, and subsequent regio-specific oxidation of intermediate penta- or tetra-sulfides with $KMnO_4$ in a mixture with $Zn(OAc)_2$ or $FeCl_3$ in order to prevent the cleavage of the final product with a base formed in the oxidation.[131] The synthesis of polysulfides **33** and **34** is shown in Scheme 3.

Scheme 3



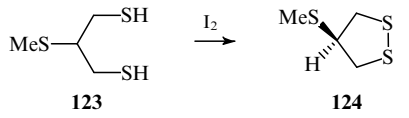
(*a*) MeLi; (*b*) $MeSCH_2SSO_2Me$; (*c*) $KMnO_4$, $Zn(OAc)_2$, $MgSO_4$, Me_2CO; (*d*) $MeSSO_2Me$; (*e*) H_2O_2, AcOH; (*f*) $KMnO_4$, $MgSO_4$, Me_2CO.

Much attention has been given to the synthesis of natural 1,2-dithiolane derivatives. The key problem in this synthesis is the formation of the dithiolane ring. To this end, reactions of 1,3-diol, ditosylate, dithiol, and dihalide derivatives with sodium disulfide, thiourea, thioacetic acid, or α-toluenethiol were employed. The use of (*N*-methoxycarbonyl-sulfamoyl)triethylammonium hydroxide for the formation of the disulfide bond has been described.[43] The interaction of the latter with 1,3-dimercaptopropan-2-ol gives 4-hydroxy-1,2-dithiolane (**122**) the oxidation of which with hydrogen peroxide results in a mixture of diastereoisomeric sulfoxides **49a**,**b** in a 4 : 1 ratio.



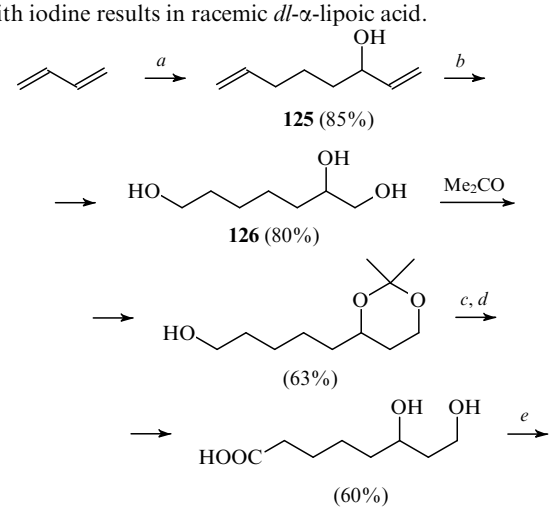
(*a*) $Et_3\overset{+}{N}SO_2\overset{-}{N}COOMe$, $CHCl_3$, 20 °C; (*b*) 0.5 N NaOH; (*c*) H_2O_2, $CHCl_3$, MeCN, 20 °C, 48 h.

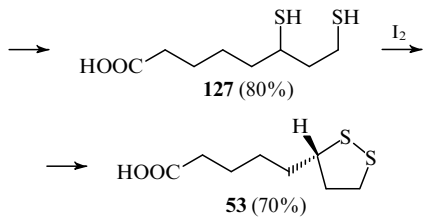
The direct oxidation of 2-methylthiopropane-1,3-dithiol (**123**) with iodine has been used in the synthesis of 4-methylthio-1,2-dithiolane (**124**) in 78% yield. The latter was isolated together with trithiane **48** from the green alga *Chara globularis*.[41]



It is interesting to note that the reaction of dithiol **123** with SCl_2 gives a mixture of cyclic sulfides **124** and **48** in a 1 : 1 ratio.[132]

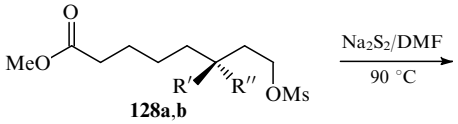
The main problem in the synthesis of lipoic acid (**53**) and its derivatives is the introduction of the side chain. A simple synthesis employing octa-1,7-dien-3-ol (**125**), which is the product of butadiene telomerisation with water [133] in the presence of palladium complexes, has been described.[134] The hydroboration of octadienol **125** with borane results in the triol (**126**); isopropylidenation of the 1,3-diol, oxidation of the free terminal hydroxy group at C(8) with the Jones reagent, methylation, deprotection, and the reaction with thiourea give the dithiol (**127**). Its oxidation with iodine results in racemic *dl*-α-lipoic acid.





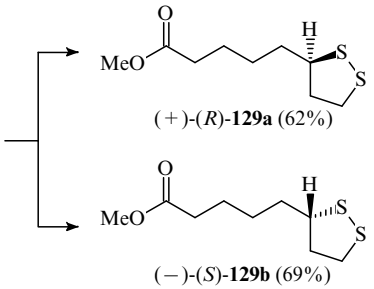
(*a*) $PdCl_2(PPh_3)_2$, H_2O, KOH; (*b*) B_2H_6, THF, H_2O_2–NaOH; (*c*) CrO_3–H_2SO_4, CH_2N_2; (*d*) H_2SO_4–MeOH; (*e*) $(NH_4)_2CS$–57% HI–NaOH.

More often, nucleophilic substitution in the corresponding 1,3-dihalides or 1,3-disulfonates is used in the synthesis of 1,2-dithiolanes. For example, methyl esters of (+)-(*R*)- and (−)-(*S*)-lipoic acids **129a**,**b** have been synthesised by the reaction of dimesylates (**128a**) or (**128b**) with sodium disulfide.[135]

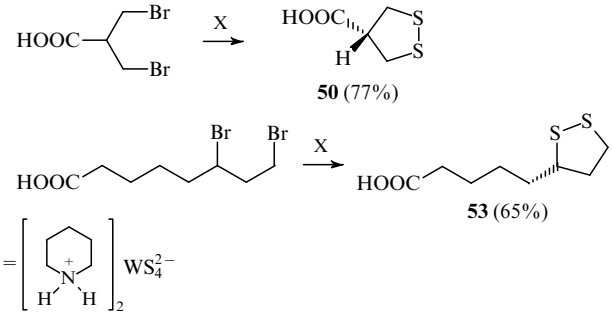


128a,**b**

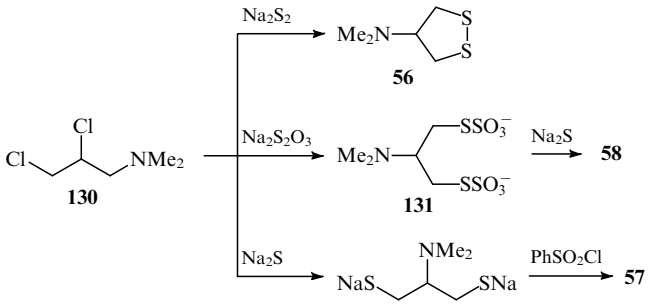
128a: R′ = H, R″ = OMs;
128b: R′ = OMs, R″ = H.



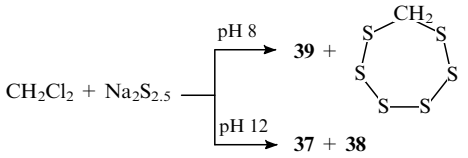
Good results in the synthesis of cyclic disulfides have been obtained with piperidinium tetrathiatungstate.[136] The latter reacts with dihalides to give the corresponding disulfides in a good yield and under mild conditions (25–40 °C, 4–5 h, DMF). This method has been used in the synthesis of (+)-lipoic acid **53** and asparagusic acid **50**.



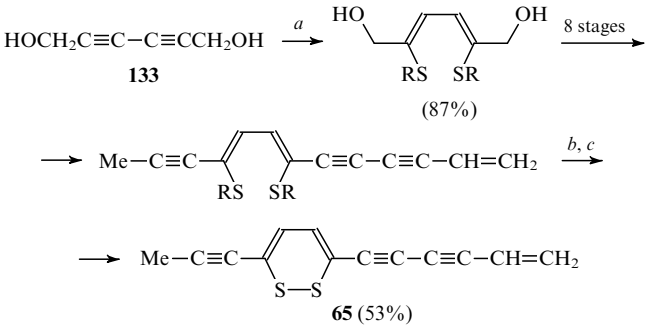
The synthesis of nereistoxin (**56**) and its analogues that are used as insecticides has a number of specific features. The dihalogenamine **130**, obtained by chlorination of allyldimethylamine is the starting compound. Under the action of sulfur nucleophiles, the amine **130** is rearranged *via* an intermediate sulfonium ion into derivatives of 1,3-dithio-substituted 2-dimethylaminopropanes. The reaction of dihalogenamine **130** with Na_2S_2 directly results in nereistoxin **56,**[137] whereas its interaction with Na_2S and then with benzenesulfonylchloride gives bensultap (**57**).[138] The treatment of 1-dimethylamino-2,3-dichloropropane (**130**) with sodium thiosulfate gives the compound **131,** which gives the trisulfide **58** upon treatment with Na_2S.[49]



Nucleophilic substitution underlies the synthesis of the pentasulfide lenthionine (**39**), trisulfide **37**, and the tetrasulfide **38** from the readily available CH_2Cl_2 and $Na_2S_{2.5}$.[139]



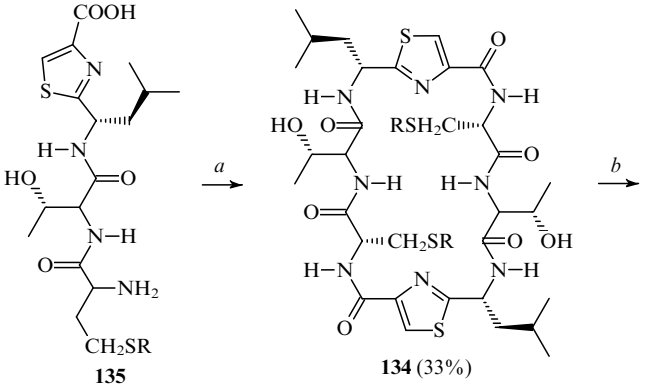
The synthesis of thiarubrin A (**65**) from hexa-2,4-diyne-1,6-diol (**133**) involves 12 steps. The use of 2-(trimethylsilyl)ethanethiol as a protecting group in the formation of the 1,2-dithiyne is noteworthy.[58]

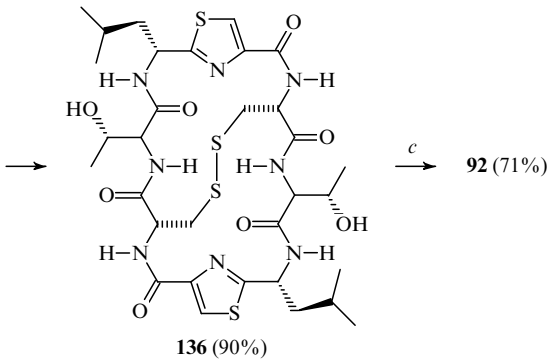


R = $Me_3SiCH_2CH_2$.

(*a*) $Me_3Si(CH_2)_2SH$, KOH – DMF, 20 °C; (*b*) Bu_4NF, molecular sieves 3 Å; (*c*) I_2, 20 °C, 30 min.

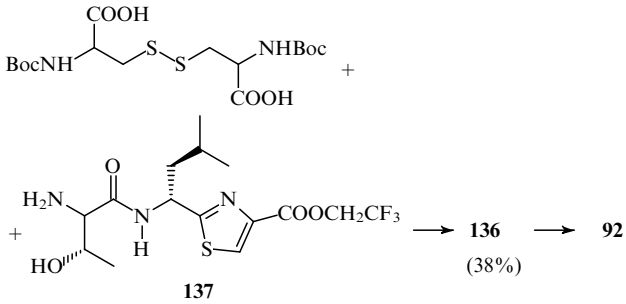
The formation of the disulfide bond upon oxidation of dithiols or their derivatives with iodine has been used in syntheses of structurally complex metabolites. Thus in the synthesis of ulthiacyclamide (**92**) it is the *S*-acetamidomethyl derivative **134** formed upon cyclodimerisation of the corresponding *S*-acetamidomethyl tripeptide (**135**) effected by diphenylphosphorazidate (DPPA) and triethylamine that undergoes oxidation with iodine.[140] The oxazole ring in the molecule **92** is formed by treatment of the intermediate disulfide **136** with an excess of thionyl chloride. This synthesis of a cytotoxin **92** competes favourably (as regards the overall yield and the number of stages) with the synthesis involving bis-cyclisation of cystine with the 2,2,2-trifluoroethyl ester **137**.[141]



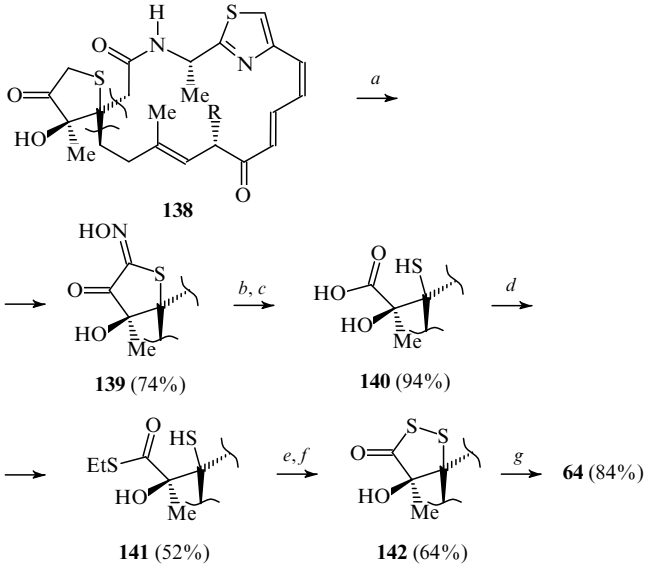


R = $CH_2NHCOMe$.

(*a*) DPPA – Et_3N, DMF; (*b*) I_2, MeOH; (*c*) $SOCl_2$, 0 °C, 17 h.



An original method for the introduction of a 1,2-dithiolan-3-one fragment as a spirofusion with aa 18-membered lactam containing a thiazole ring has been offered in Ref.[142]. The nitrosylation of thiolanone **138** gives the oxime **139**. Subsequent protection of the keto group of the dienone fragment as the *O*-methyloxime followed by Beckmann rearrangement under the action of 2,6-dimethylbenzoyl chloride results in a mercapto acid **140,** which was further converted into the thioester **141**. Treatment of the latter with sodium hydrogen sulfide and iodine with subsequent deprotection are followed by cyclisation leading to (*S*)-deoxyleunamycin (**142**), which is stereoselectively oxidised into (+)-leinamycin (**64**).



R = OCH_2OMe.

(*a*) Am^iONO, NaOMe, 23 °C, 1.5 h; (*b*) $MeONH_2 \cdot HCl$, Py;

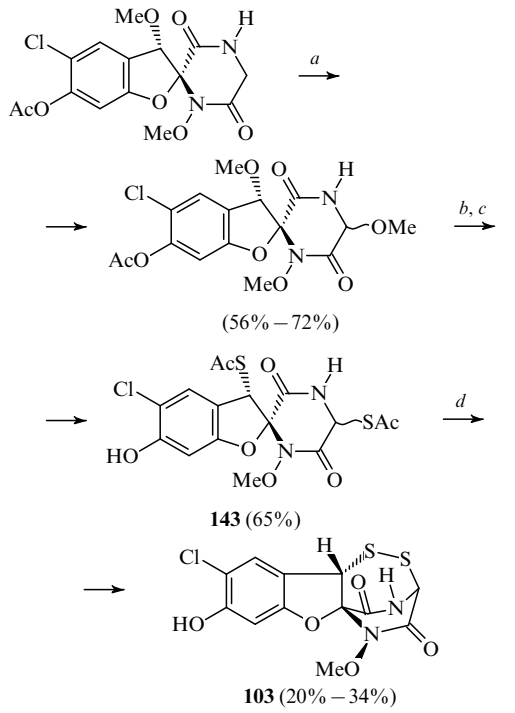
(*c*) 2,6-$Me_2C_6H_3COCl$, Py; (*d*) EtSH, THF, 20 °C, 20 min;

(*e*) NaSH, THF, I_2, 10 min; (*f*) 33% HCHO, 3 N HCl, Me_2CO;

(*g*) 3-$ClC_6H_4CO_3H$, THF, 0 °C, 45 min.

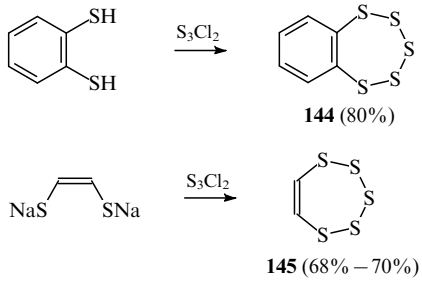
The total synthesis of the disulfide antibiotic aspirochlorine (**103**) from 4-chlororesorcinol includes 14 stages. The most notable are the final steps shown in Scheme 4. The methoxy group is introduced into the piperazinedione ring by treatment with *tert*-butyl hypochlorite in methanol in the presence of sodium methoxide. This is followed by substitution of two methoxy groups for the acetylthio groups under the action of thioacetic acid in the presence of boron trifluoride etherate. And, finally, the closure of the disulfide bridge is performed by treatment of bisthioacetate **143** with *O*-methylhydroxylamine and camphorsulphonic acid.[114]

Scheme 4

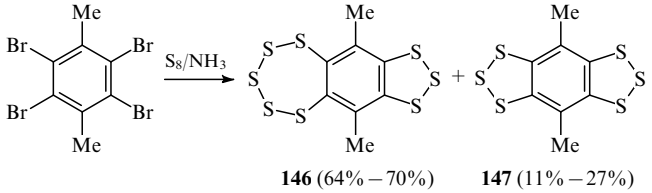


(*a*) Bu^{t}OCl, NaOMe; (*b*) NaOEt – EtOH; (*c*) AcSH, $BF_3 \cdot Et_2O$;
(*d*) $MeONH_2$, d-camphorsulphonic acid, THF, 23 °C.

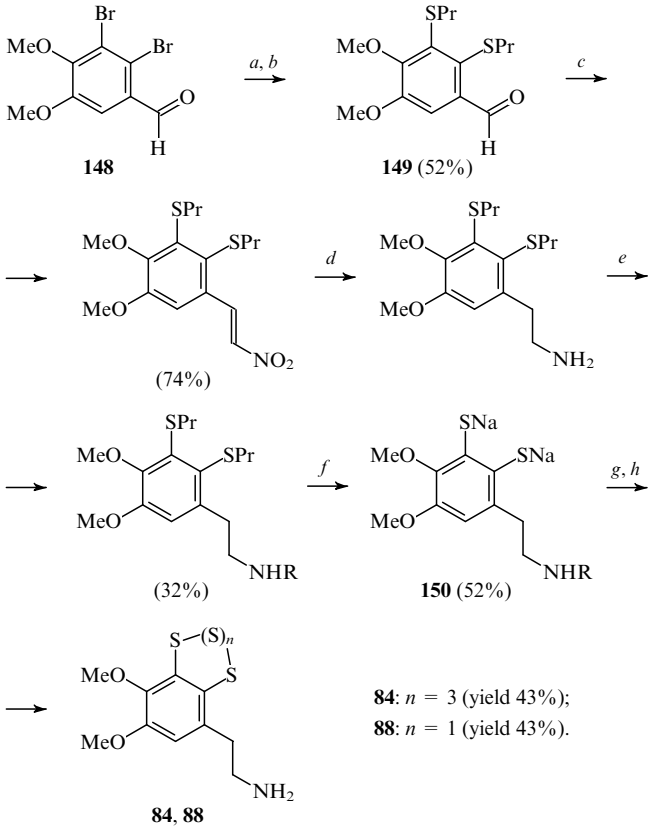
Considerable attention has been paid to the synthesis of benzopentathiepine **144** and its analogue **145**. Benzopentathiepine is formed by treatment of benzene-1,2-dithiol with S_3Cl_2 in ether, the yield being up to 80%.[143, 144] An analogous scheme is used to obtain pentathiepine **145**.



An interesting method for the introduction of a pentathiepine fragment[145] is based on the reaction of aromatic *o*-dibromides with sulfur in liquid ammonia. In this case, trisulfide derivatives **147** are formed along with the main reaction product **146**.



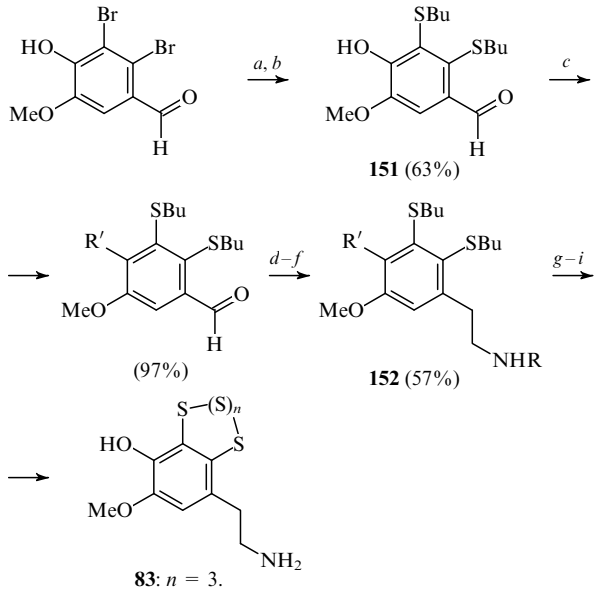
The interest in the synthesis of varacin (**84**) and lissoclinotoxins (**81** – **83**) is explained primarily by their valuable biological activity. Schemes of total synthesis of varacin (**84**) and isolissoclinotoxin (**83**) from vanillin in which the pentasulfide fragment was prepared from *o*-dimercaptobenzenes are described. Thus the treatment of 2,3-dibromoveratric aldehyde **148,** which was obtained from vanillin, with copper propanethiolate and remethylation of hydroxy groups resulting from partial demethylation of methoxy groups gave the dipropylthio derivative **149**.[146] This was followed by the reaction of **149** with nitromethane, reduction of the nitro group with lithium aluminium hydride, and protection of the resulting amino group. Splitting of the thioester groups with sodium in ammonia and the reaction of disodium dithiolate **150** with S_2Cl_2 gives a mixture of benzotrithiole and benzopentathiepine **84** in a total yield of 86%. The final stage is non-selective, because trisulfide **88** is formed along with varacin **84** in a 1 : 1 ratio.



R = TEOC.

(*a*) PrSCu, quinoline – Py, 160 °C; (*b*) $(MeO)_2SO_2 - K_2CO_3$, Bu^n_4NI, $CH_2Cl_2 - H_2O$; (*c*) $MeNO_2$, NH_4OAc/AcOH, 23 °C; (*d*) $LiAlH_4$, THF, 65 °C, 25 min; *e*) 4-$NO_2C_6H_4OR$, $Et_3N - CH_2Cl_2$; (*f*) Na/NH_3; (*g*) S_2Cl_2 – THF, 25 °C, 45 min; (*h*) CF_3COOH, $CHCl_3$, 20 °C, 50 min.

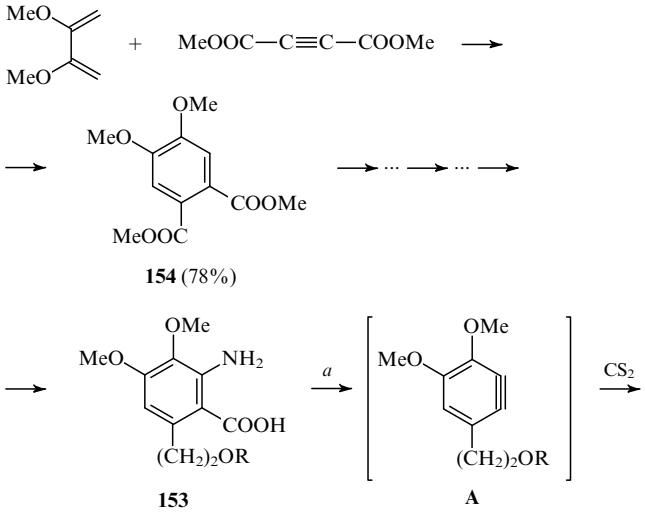
The key step in the synthesis of isolissoclinotoxin A (**83**) is the reaction of 5,6-dibromovanillin with copper butanethiolate resulting in the dithioether **151**.[147] The protection of the phenolic hydroxyl at position 4 with methoxymethyl chloride and subsequent introduction of the nitrogen-containing substituent according to the aforementioned reaction sequence give compound **152**. Reduction of the *o*-butylthio groups with sodium in ammonia and subsequent treatment of the dithiolate anion with S_2Cl_2 give a mixture of penta- and tri-sulfides in a 2.4 : 1 ratio.

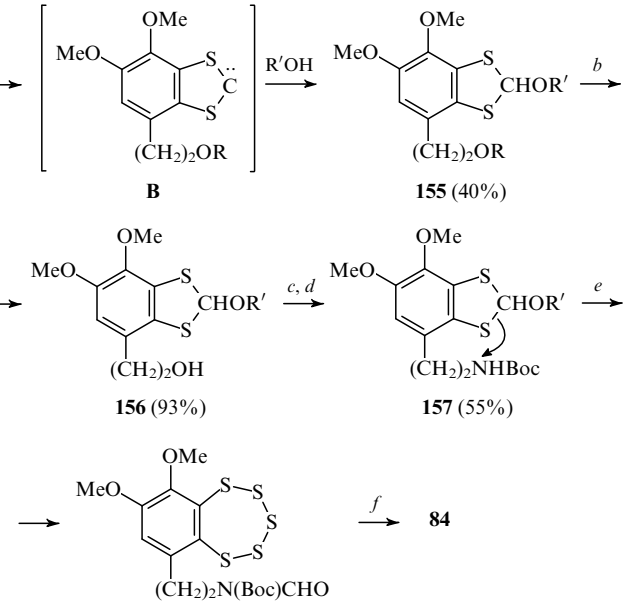


R = $CO(CH_2)_2SiMe_3$; R′ = CH_2OMe; n = 1, 3.

(*a*) Bu^nSCu, quinoline–Py, 160 °C; (*b*) $(MeO)_2SO_2-K_2CO_3$, Bu^n_4NI, $CH_2Cl_2-H_2O$; (*c*) CH_2ClOMe, Pr_2NEt, CH_2Cl_2, 23 °C; (*d*) $MeNO_2$, NH_4OAc/AcOH; (*e*) $LiAlH_4$, THF, 65 °C, 25 min; (*f*) 4-$NO_2C_6H_4OR$, $Et_3N-CH_2Cl_2$; (*g*) Na/NH_3 (yield 50%); (*h*) S_2Cl_2–THF, 25 °C, 45 min (yield 67%); (*i*) CF_3COOH, $CHCl_3$, 20 °C, 50 min (yield 86%);

In the scheme of the synthesis of varacin (**84**),[148] of special note is the approach allowing selective introduction of a pentasulfide fragment. The initial product is the substituted anthranilic acid **153** which is readily formed from diester **154**. Treatment of the acid **153** with isopentyl nitrite in the presence of carbonic sulfide and isopentyl alcohol gave cyclic dithioether **155** formed *via* intermediates **A** and **B**. In order to introduce the nitrogen-containing substituent, silyl protection was removed and the alcohol formed **156** was introduced into the reaction with phthalimide. Splitting of the phthaloyl protection by hydrazinolysis resulted in a free amino group further protected as a BOC derivative to give the compound **157**. Treatment of the latter with S_2Cl_2 cleaves the orthoester and yields the pentathiepine ring. It is of note that the transfer of the formyl residue from the sulfur-containing to the nitrogen-containing substituent occurs in the course of pentathiepine **158** formation.





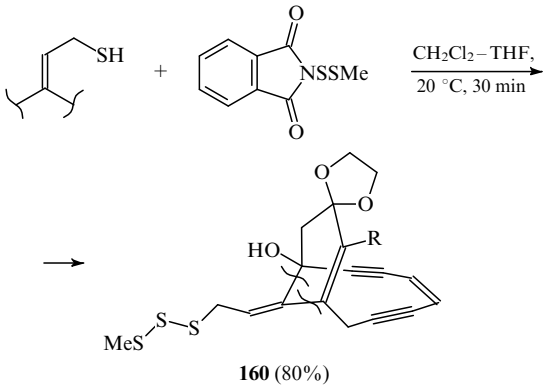
R = Bu^tPh_2Si; R′ = $Pent^i$.

(*a*) $Pent^iONO$, PentOH, CS_2, CH_2Cl_2, 75 °C, 30 min; (*b*) Bu_4NF, THF, 23 °C, 30 min; (*c*) phthalimide, EtOOCN=NCOOEt, PPh_3, THF, 25 °C, 27 h; (*d*) N_2H_4, EtOH, $(Boc)_2O$, 4-$Me_2NC_5H_4N$, CH_2Cl_2; (*e*) S_2Cl_2, THF, 20 °C, 25 min; (*f*) HCl–MeOH.

The conversion of the easily accessible disulfide glyotoxin **99** into the tetrasulfide glyotoxin G **102** was effected by treatment with sulfur and lithium α-toluenethiolate (0.1 equivalent) in CS_2.[112]

99 $\xrightarrow[PhCH_2SLi]{S_8/CS_2,}$ **102** (60%)

An increasing number of papers have been dedicated to the synthesis of calichemycin (**94**) and esperamycins (**96**–**98**). The introduction of the trisulfide fragment is not a challenging task. For example, the synthesis of a model compound **160** from the corresponding thiol was carried out by a standard procedure.[149]



160 (80%)

R = NHCOOMe.

The references[150–156] are related to the total synthesis of sulfur-containing enediyne antibiotics and their fragments.

IV. Conclusion

As can be seen from the data presented, the natural polysulfides constitute a promising group of low-molecular-weight bioregulators. The chemistry of many of them is of substantial interest.

Thus the long-standing controversies about the nature of the biologically active substances of onion and garlic have been

resolved only very recently and required the use of sophisticated analytical procedures. One cannot but mention in this connection the promising studies dedicated to the modelling of structures of biologically active components of garlic.

There is no doubt that the knowledge of the mechanisms of action of unique trisulfide enediyne antibiotics will open up new routes in the search for inhibitors of growth of malignant tumours.

Some polysulfides of marine organisms draw attention with a combination of high biological activity and relatively simple structures. Taking into account the present-day level of organic synthesis, it may be thought that further development of technological methods for the synthesis of the most promising natural compounds and their active analogues is quite a realistic task. In this respect an appropriate example is the organisation of the large-scale manufacture of a selective insecticide bensultap, an analogue of the natural insecticide nereistoxin.

It is thought that keen attention of synthetic chemists will be drawn to natural aromatic polysulfides and dithiin derivatives possessing high antitumour activity.

Thus the chemistry of natural polysulfides offers a vast field for specialists in organic synthesis, who are interested in the synthesis of complex structures, as well as for all those who are engaged in the design of biologically active compounds.

The material presented herein prompts a conclusion that further developments in the field of chemistry and biochemistry of natural polysulfides and their analogues will have consequences which are valuable from the practical point of view for medicine and agriculture. Also of significance is the acquisition of fundamental knowledge of the reactivity and stereochemistry of sulfur-containing cyclic systems.

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