Pentathiepins

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1. Introduction

The only possible seven-membered ring compounds containing a carbon−carbon double bond and five sulfur atoms are 1,2,3,4,5-pentathiepin **1** and its derivatives. Many examples of the saturated system, 1,2,3,4,5-pentathiepan, and the 1,2,3,4,6- and 1,2,3,5,6-isomers are known, but these are not covered in this review. Pentathiepins have attracted much attention since the first preparation of **1** (Figure 1) and

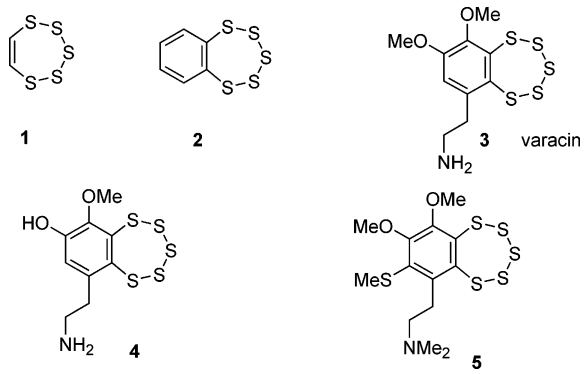

Figure 1.

benzopentathiepin **2** by Fehér in 1971[1] because of their remarkable stability, the high energy barrier for inversion of the chairlike polysulfur ring, their occurrence in Nature, and their potent biological activity. The first naturally occurring examples, varacin **3**, lissoclinotoxin A **4**, and *N*,*N*-dimethyl-5-(methylthio)varacin **5**, have strong antimicrobial and antifungal activity and selectively inhibit protein kinase C, and varacin is highly toxic toward human colon cancer (see section 6). The polysulfur ring of these benzopentathiepin antibiotics appears to be crucial for the biological activity.

There are no reviews devoted exclusively to pentathiepins, though they are included in combined reviews in *Comprehensive Heterocyclic Chemistry*.[2]

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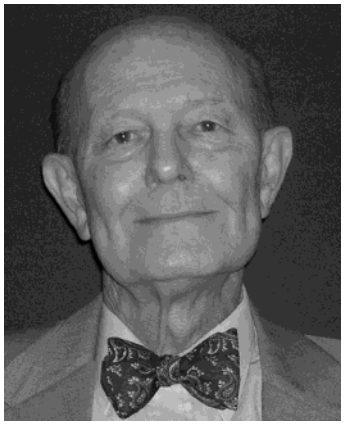
Lidia Konstantinova was born in the Kemerovo region, Russia. She graduated from the M. V. Lomonosov Moscow Institute of Fine Chemical Technology and then started work at the N. D. Zelinsky Institute of Organic Chemistry, where she is a Senior Researcher at the present time. In 1994 she received her Ph.D. degree for synthesis and investigation of properties of new heterocyclic 1,2,5-oxadiazoles. Since 1995 her research interests are in the synthesis of polysulfur–nitrogen heterocyclic systems, including pentathiepins condensed with other sulfur and nitrogen heterocycles.

Oleg Rakitin was born in Moscow in 1952 and studied at M. V. Lomonosov Moscow State University, where he graduated in 1974. He has been a Junior Researcher (1974–1982), Senior Researcher (1982–1994), Principal Researcher (1994–1995), and since 1995 Head of the Laboratory at N. D. Zelinsky Institute of Organic Chemistry. He received his Ph.D. degree in 1980 and his Doctor of Science in 1992. He has spent a few months in the laboratory of Professor C. W. Rees at Imperial College (London, U.K.) and was awarded a Royal Society Kapitza Fellowship (1992), a Royal Society of Chemistry Journals Grant for International Authors (1997, 2000), and Royal Society Joint Projects (1993, 1999, 2002). He has been a Fellow of the Royal Society of Chemistry since 1999. His scientific interests include the synthesis and chemistry of nitrogen and sulfur heterocyclic compounds, particularly polysulfur heterocycles.



Charles W. Rees, C.B.E., F.R.S. is an Emeritus Professor and Senior Research Fellow at Imperial College, London, where he previously held the Hofmann Chair of Organic Chemistry. He has nearly 50 years' experience of academic teaching and research in the Universities of London, Leicester, and Liverpool and has, for 40 years, been an active consultant to the fine chemical industry. His research has centered on the synthesis and chemistry of heterocyclic compounds with an emphasis on aromatic and antiaromatic systems and the role of reactive intermediates in heterocyclic chemistry. Recently, he has been working on heterocyclics with an unusually high proportion of nitrogen and sulfur heteroatoms. He has published over 400 papers in the scientific literature, has many honors and awards, and was President of the Royal Society of Chemistry from 1992 to 1994.

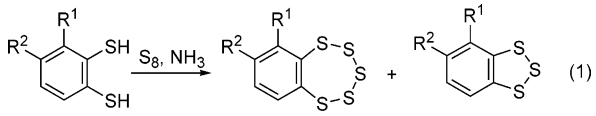
This comprehensive review covers the literature up to late 2003 and *Chemical Abstracts* up to Vol. 136.

2. Synthesis

2.1. From Elemental Sulfur and *ortho*-Disubstituted Compounds

2.1.1. From ortho-Dithiols

Sato described the synthesis of benzopentathiepin **2** and its 7-chloro derivative, **7b**, by treatment of 1,2-benzenedithiols **6** (and their dithiolothiones, see next section) with sulfur and liquid ammonia at 20 °C in a titanium autoclave.[3]



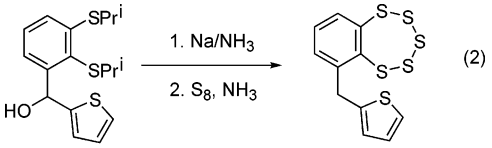
(1)

6 **7** **8**

a. $R^1 = R^2 = H$; **b.** $R^1 = H$, $R^2 = Cl$; **c.** $R^1 = SiMe_3$, $R^2 = H$; **d.** $R^1 = SiMe_2Bu^t$, $R^2 = H$; **e.** $R^1 = SiEt_3$, $R^2 = H$; **f.** $R^1 = SiPh_3$, $R^2 = H$; **g.** $R^1 = R^2 = MeO$; **h.** $R^1 = CH_2CH_2NHBoc$, $R^2 = H$; **i.** $R^1 = CH_2Py\text{-}2$, $R^2 = H$; **j.** $R^1 = CH_2$pyrimidyl-2, $R^2 = H$;

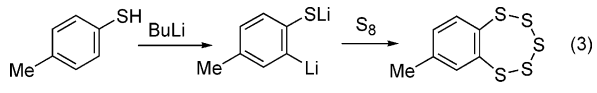
The procedure was developed further using gaseous ammonia in dichloromethane as solvent, and the yields were excellent.[4−6] 6,7-Dimethoxybenzopentathiepin **7g** and 6-(2-aminoethyl)benzopentathiepin **7** ($R^1 = CH_2CH_2NH_2$; $R^2 = H$), partial structures of the antibiotic varacin **3**, have been synthesized in this way from the corresponding benzenedithiols and their biological activity determined (see section 6).[5] More crowded benzenedithiols gave the corresponding trithioles **8** as minor products, but pentathiepins are normally the thermodynamically favored products.

S,*S*-Dialkyl derivatives of **6** can also be used in this reaction. Thus, **9** was dealkylated and reduced with sodium in liquid ammonia, followed by treatment with sulfur in the same medium, to give **10**.[6] However 1,2,4,5-tetrathiolo-3,6-bis(isopropyloxy)benzene gave only unidentified polymer under the same conditions.[7a] The extensive contributions of the Sato group to the synthesis and chemistry of benzopentathiepins and their extension to analogous selenium compounds have been recently summarized.[7b]



9 **10**, 34%

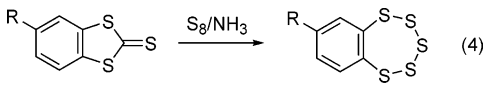
Another way in which an *ortho*-dithiol dianion intermediate was (presumably) generated in situ was by conversion of *p*-toluenethiol into its dithio derivative **11** with butyllithium followed by treatment with sulfur to give pentathiepin **12** (59%).[8]



11 **12**

2.1.2. From Fused 1,3-Dithiole-2-thiones

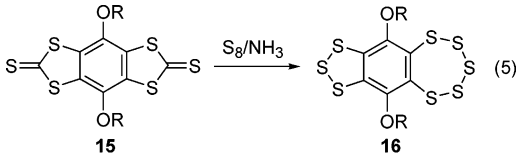
A number of fused pentathiepins has been synthesized by Sato and co-workers in moderate to excellent yields from 1,3-dithiole-2-thiones **13**, sulfur, and ammonia.[3] The best yields were obtained with benzene as solvent; however, 7-nitrobenzopentathiepin was not obtained by this method from **13**, R = NO_2. It is interesting that pentathiepin **14a** was isolated in better yield from **13a** than from dithiol **6a**, which is obtained by hydrolysis of **13a** and is considered to be an intermediate in the preparation of **14a**.



13 **14**

a. R = H (82%), **b**. R = Cl (59%),
c. R = OMe (99%), **d**. R = NH_2 (91%)

With sulfur in liquid ammonia, the bis-dithiolothiones **15** did not give the analogous bis-pentathiepins but rather the monotrithiolo-monopentathiepins **16**, mostly in very high yields.[7] Bis-pentathiepins are not inherently unstable (see section 2.3.2), but the trithiolo products **16** may be favored by reduced steric compression in these hexasubstituted benzenes. Note that the benzo-bispentathiepins that could have been formed here would be more sterically congested than compound **66** (section 2.3.2) with its central five-membered ring. Unfortunately the bis-dithiolothione **15**, but without the alkoxy groups, gave unidentified polymer rather than any cyclic polysulfides under the same conditions.

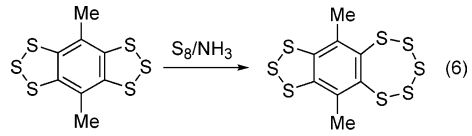


15 **16**

a. R = Me (82%), **b**. R = Et (99%),
c. R = Pr^i (99%), **d**. R = $PhCH_2$ (62%)

2.1.3. From 1,2,3-Trithioles

As we have seen, benzotrithioles are common byproducts in pentathiepin formation from *ortho*-disubstituted benzenes. The five- and seven-membered heterocyclic rings are interconvertible in the reaction mixtures, and pentathiepin **18** can be prepared from trithiole **17** in good yield upon treatment with sulfur in liquid ammonia.[9]

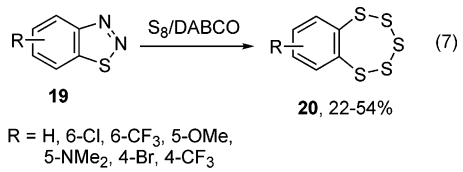


17 **18**, 78%

2.1.4. From 1,2,3-Thiadiazoles

This method was discovered and developed by Chenard and co-workers.[10,11] A series of benzopentathiepins **20** was obtained by heating the benzothiadiazoles **19** with sulfur in decalin at 160−185 °C. It was found that diazabicyclo[2.2.2]octane (DABCO) was uniquely beneficial in increasing the reaction yields, possibly because of its high nucleophilic reactivity in opening the S_8 rings. The benzothiadiazoles are presumably reacting as masked diazonium sulfides, the diazonium group being displaced by an activated S_8-DABCO intermediate.

This method was extended to the same transformation of heterocyclic fused 1,2,3-thiadiazoles to form the pyrazolo-[11] and dihydrofuro-[12]pentathiepins **21** and **22**.

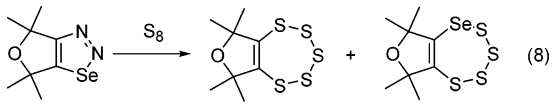


19 **20**, 22-54%

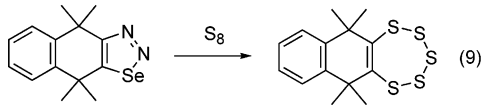
R = H, 6-Cl, 6-CF_3, 5-OMe, 5-NMe_2, 4-Br, 4-CF_3

21, R = H, Br, CO_2Et, 36-44% **22**, 22%

1,2,3-Selenodiazoles **23** and **26** similarly gave the pentathiepins **24** and **27**, respectively, but 1-seleno-2,3,4,5-tetrathiepins **25** was also isolated.[13]



23 **24**, 10% **25**, 19%

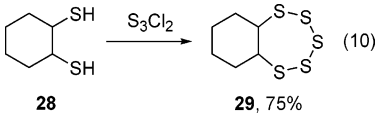


26 **27**, 25%

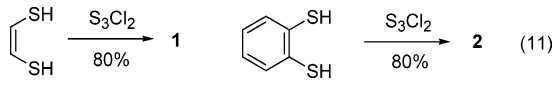
2.2. From *ortho*-Disubstituted Compounds and Other Reagents

One of the simplest routes to pentathiepins is the reaction of a 1,2-dithiol or its salts with disulfur dichloride, S_2Cl_2; again, the dithiol may also be generated in situ.

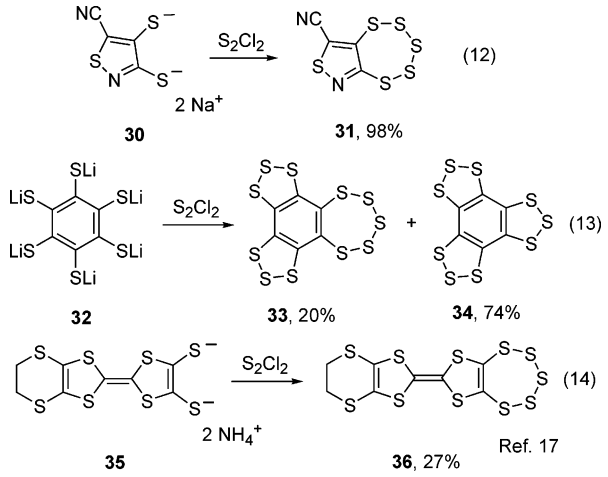
The first known pentathiepin derivative, cyclohexapentathiepan **29**, was prepared in 1967 by Fehér and Degen by reacting *trans*-cyclohexan-1,2-dithiol **28** with dichlorotrisulfane, S_3Cl_2.[14] This reaction was then extended to the synthesis of pentathiepins with replacement of S_3Cl_2 by the much more readily available and stable S_2Cl_2.



Disproportionation between the polysulfur species involved usually ensures that the sole or major product is the stable pentathiepin. This method is limited only by the availability and stability of the bismercapto starting material. *cis*-Ethene-1,2-dithiol and benzene-1,2-dithiol with S_3Cl_2 gave the parent pentathiepin **1** and benzopentathiepin **2**.[1]



Some more examples where the starting material is a salt of the dithiol are shown in eqs 12−14. The isothiazolopentathiepin **31** is formed almost quantitatively;[15] with hexalithium hexamercaptobenzene **32,** the combined yield of products is also very high but the major product is the tristrithiole **34**.[16] Only one pentathiepin ring is formed, the trithiole rings being favored, once more, in this crowded situation.

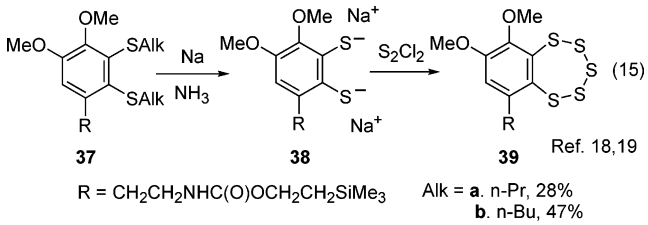


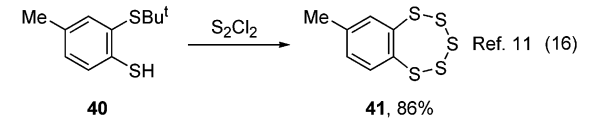
Further examples of this reaction where the dithiolate is generated in situ are shown in eqs 15−21.[8,11,18−23]

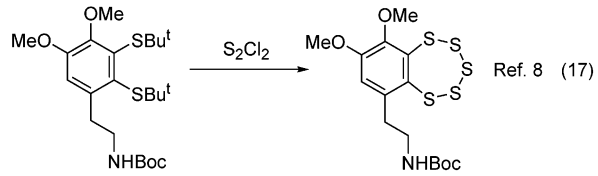
2.3. Cyclosulfurization across Carbon−Carbon Bonds

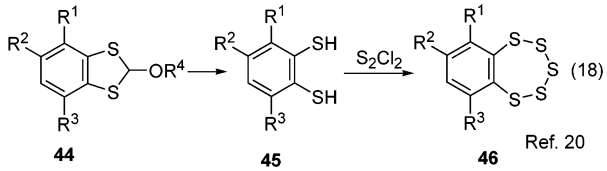
2.3.1. With Sulfur

While heating alkenes with elemental sulfur provides a route to the saturated pentathiepans, often in low yield, pentathiepin formation has not been reported in these simple reactions. There are a few examples of such cyclosulfurizations across various carbon−carbon bonds. Heating *N*-methylhexahydroazepine **56** with sulfur in HMPA gave the pentathiepinopyrrole **57** in low yield, among other polysulfides.[24]

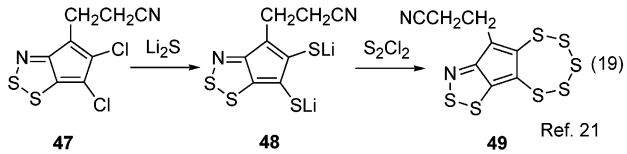


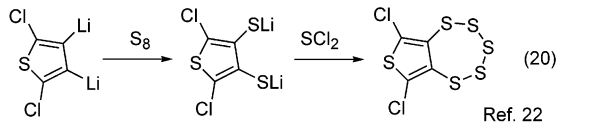


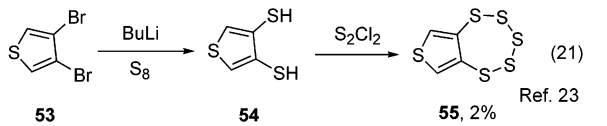




a. $R^1 = R^2 = R^3 = H$, $R^4 = Bu$
b. $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Bu$
c. $R^1 = R^2 = OMe$, $R^3 = CH_2CH_2NHBoc$, $R^4 = CH_2CH_2CMe_2$

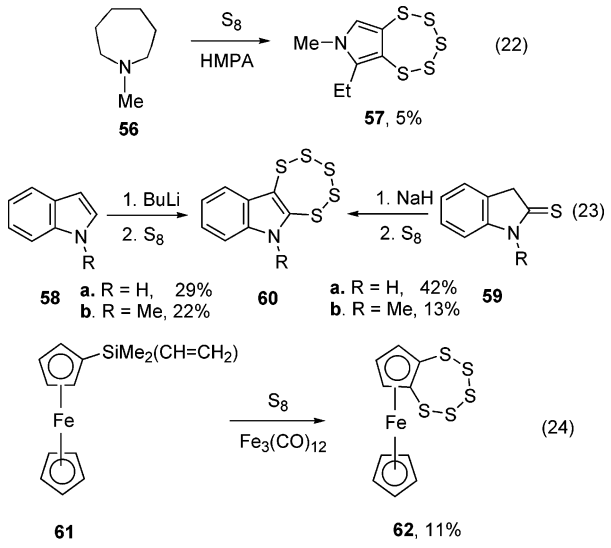






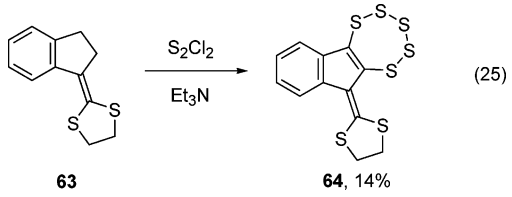
Milder and higher yielding routes to indolopentathiepins **60** have been developed by Bergman and co-workers from the indole derivatives **58** and **59**.[25a] Similar treatment of benzo[*b*]thiophene with butyllithium and S_8 gave the exactly analogous benzothiophenopentathiepin (28%), though benzo[*b*]furan gave a bisbenzofuranotetrathiocine (analogous to **97** instead).[25b]

The combination of S_8 with $Fe_3(CO)_{12}$ converted the silylferrocene **61** into pentathiepin **62** in low yield in a complex reaction.[26a] The same compound was prepared in much higher yield by treatment of the 2,2-dimethyl-1,3,2-dithiastannole derivative of ferrocene-1,2-dithiol with sulfur dichloride, and its spectroscopic and X-ray diffraction properties were described.[26b]

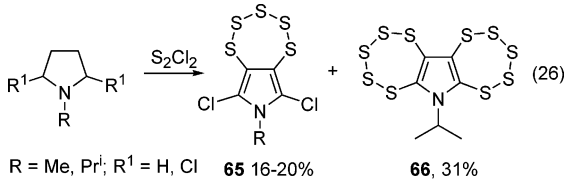


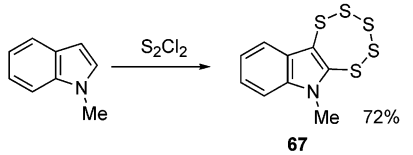
2.3.2. With Disulfur Dichloride

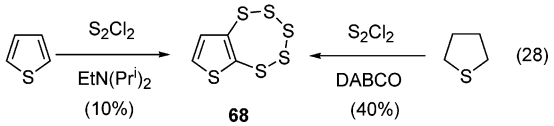
Commercially available disulfur dichloride, S_2Cl_2, appears to be the most promising reagent for this transformation. With triethylamine in toluene, it converted the indane derivative **63**, which is probably activated by the enedithio group, into pentathiepin **64**, albeit in low yield.[27]



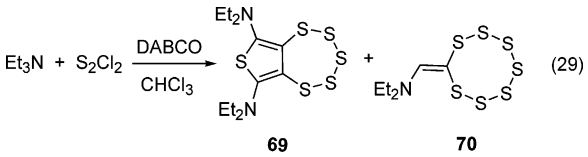
We recently showed that treatment of nucleophilic heterocycles such as pyrroles and thiophene and their tetrahydro derivatives with S_2Cl_2 and a base provides a simple one-pot synthesis of heterocyclic fused pentathiepins, sometimes in surprisingly good yields (eqs 26−28).[28] Compound **66** from *N*-isopropylpyrrolidine, S_2Cl_2, and DABCO is the first bispentathiepin reported (see section 2.1.2).







Even more curious and unexpected reactions were observed when S_2Cl_2 and DABCO were premixed in chloroform at 0 °C for 48 h followed by the addition of Et_3N and heating the mixture.[29] The thienopentathiepin **69** (30%) together with the heptathiocane **70** (10%) was produced; their polysulfur rings had the expected chair and crown conformations, respectively.

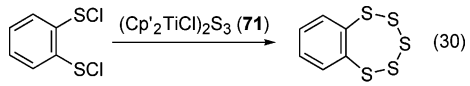


The same reactions were observed with other tertiary *N*-ethylamines but in lower yields. Although yields are mostly low, the products are prepared in one pot from cheap starting materials.

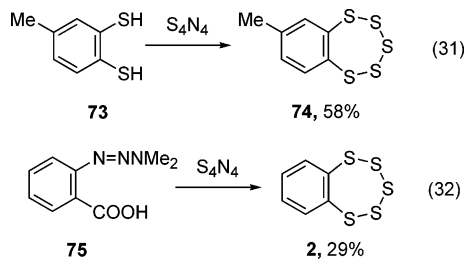
The thiophene ring of **69** has been created from two ethyl groups, with a new C−C bond being formed between two, formally unactivated, methyl groups; a pentathiepin ring has been fused onto the thiophene as in the above transformations (eqs 26−28). Mechanisms were proposed for all these S_2Cl_2 reactions.

2.4. Miscellaneous Methods

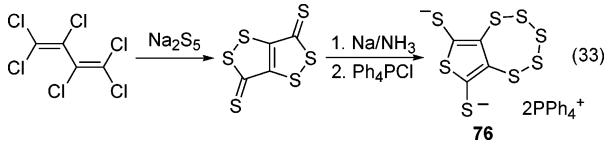
Finally, some miscellaneous preparations of pentathiepins are described, most of which were discovered by chance. One rational method, however, is the insertion of three sulfur atoms into benzene-1,2-bis(sulfenyl chloride) **72** with bis(bis(pentamethylcyclopentadienyl))chlorotitanium trisulfide **71**, which gave benzopentathiepin **2** in good yield.[30]



Benzopentathiepins were formed in two curious reactions of tetrasulfur tetranitride, S_4N_4, in boiling xylene, with 4-methylbenzene-1,2-dithiol **73** and the benzyne precursor **75**.[31]

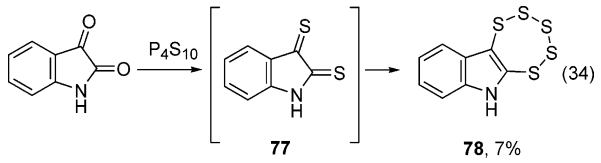


Perchloro-1,3-butadiene reacts with Na_2S_5 to give a bis(dithiolothione),[32a] which on reduction with sodium in liquid ammonia and treatment with $Ph_4P^+Cl^-$ gave the thiophenopentathiepin **76** (69%) (eq 33).[32b]

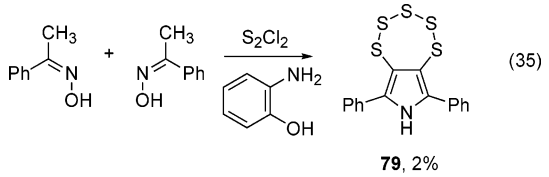


An attempted formation of isatindithione **77** from isatin and P_4S_{10} in boiling pyridine gave a low yield

of pentathiepinoindole **78**, possibly via the dithione **77**, again indicating a pentathiepin as the thermodynamically stable end product.[33]



In a curious and completely unexpected reaction, the pyrrolopentathiepin **79** was found as a very minor byproduct of the reaction of acetophenone oxime and S_2Cl_2 in the presence of pyridine and *o*-aminophenol.[34] A possible mechanism was suggested.

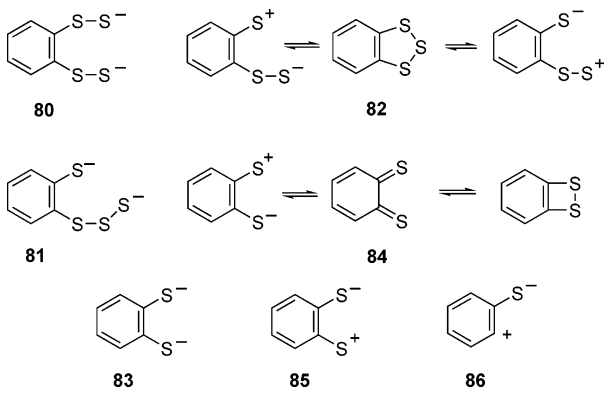


3. Reactions of the Pentasulfur Rings

Relatively few monocyclic pentathiepins are known, and very little of their chemistry has been explored. The more readily available bicyclic and tricyclic derivatives have been quite widely investigated and shown to display a varied chemistry. In this section we deal with reactions of the S_5 rings and in the next section with reactions of the attached rings and their substituents. The former class is dominated by the loss of one to all five of the sulfur atoms. Mostly commonly, 3 sulfur atoms are extruded, followed by 4 > 2 > 1, 5. In the second group of reactions the polysulfur rings remain intact, thus demonstrating their stability toward quite vigorous reaction conditions.

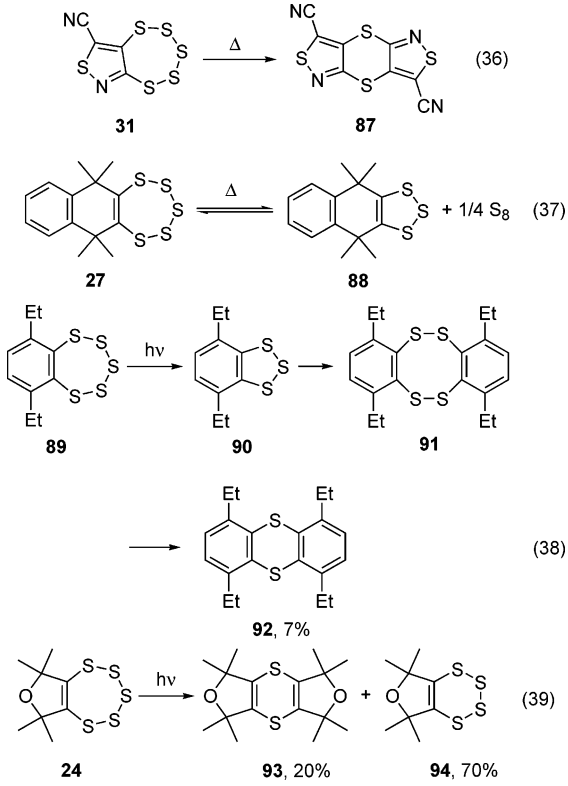
The many reactions observed for fused pentathiepins result from the various possibilities of ready nucleophilic or electrophilic attack at sulfur, with opening of the heterocyclic ring and loss of sulfur atoms. These reactions can be envisaged, formally at least, as involving various intermediates,[35] such as those shown in Scheme 1, and several are the formal reverse of the pentathiepin-forming reactions described in section 2.

Scheme 1. Possible Intermediates in Benzopentathiepin Reactions



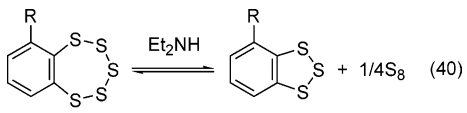
3.1. Thermolysis and Photolysis

These reactions involve the loss of 2, 3, or 4 sulfur atoms to give, respectively, 1,2,3-trithioles, dimeric tetrathiocines, and 1,4-dithiins. Thus, "pyrolysis" of isothiazolopentathiepin **31** gave **87**;[15] heating pentathiepin **27** in 1,2-dichlorobenzene at 140 °C or irradiation gave an equilibrated mixture of **27**, **88**, and sulfur.[36] Irradiation of diethylbenzopentathiepin **89** in DCM proceeded by consecutive desulfurization, dimerization, and ring contraction to give trithiole **90**, tetrathiocin **91**, and finally dithiin **92**.[37] Dihydrofuranopentathiepin **24** gave the analogous dithiin **93** (20%) together with a rare 1,2,3,4-tetrathiin **94** (70%) as the major photolysis product.[12]



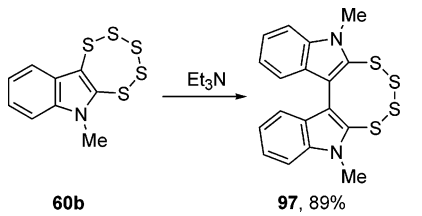
3.2. Desulfurization with Bases

Treatment of pentathiepins with secondary and tertiary amines and with DBU also causes desulfurization with loss of 2, 3, 4, or 5 sulfur atoms. *ortho*-Substituted benzopentathiepins **95** with diethylamine in hexane gave the corresponding trithioles **96**.[11] With the trifluoromethyl compound the equilibrium could also be established from the trithiole **96a** and sulfur in the presence of diethylamine. Electron withdrawal by the substituent was thought to be more important than its size in stabilizing the trithiole.



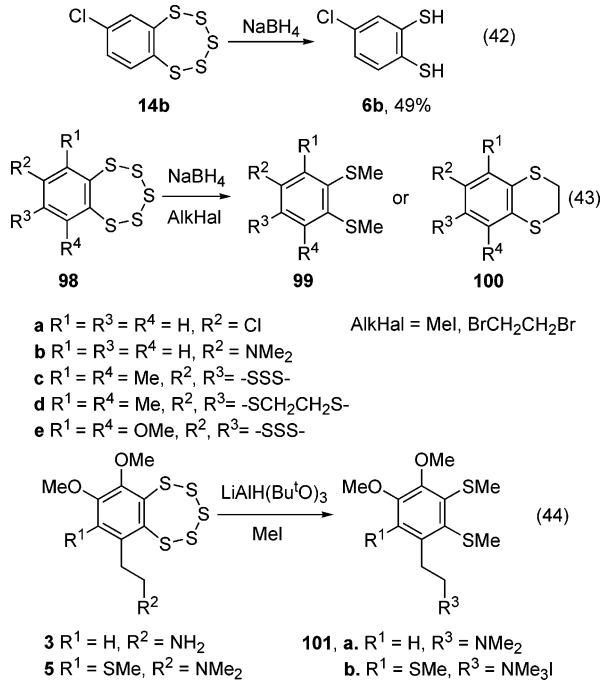
R = **a**. CF_3, **b**. Br, **c**. CH_2CO_2Me

Heating pentathiepinoindole **60b** with Et_3N in ethanol gave a remarkably high yield of the dimeric 1,2,3,4-tetrathiocin **97** in a mechanistically intriguing reaction in which the dithioisatin may have been an intermediate.[25a]



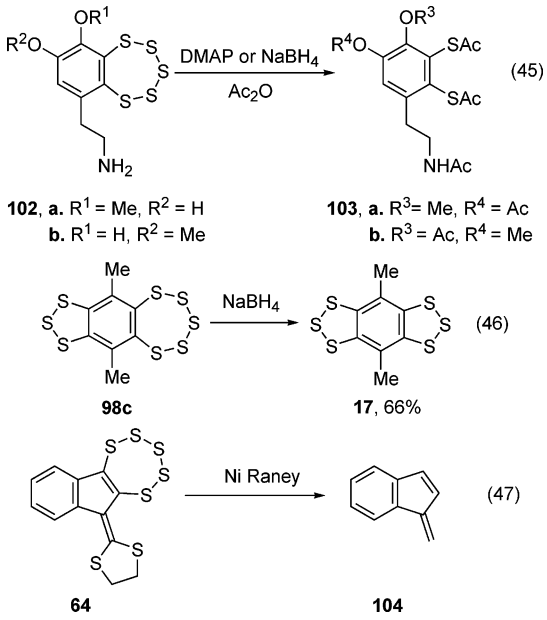
3.3. Reduction

The most common reagent for reduction of pentathiepins is sodium borohydride,[11] often followed by in situ alkylation, e.g., with iodomethane, to make the bisdithiol products more tractable. Thus, benzopentathiepin **14b** gave **6b** and benzopentathiepins **98** gave **99** or **100**.[7,9,11] Pentathiepinoindole **67** (eq 27) similarly gave the 2,3-bis(methylthio)indole (44%).[25a] Lithium tri(*tert*-butoxy)aluminum hydride, followed by iodomethane, was used for the same reduction of varacin **3** and its analogue **5**.[38,39]



Overall reduction and acetylation of lissoclinotoxin A **4** was effected by treatment with DMAP and acetic anhydride in DMF at room temperature;[40] possibly the three sulfur atoms are removed by nucleophilic attack on sulfur by DMAP, ultimately to give S_8. Isolissoclinotoxin A **102b** was similarly transformed into **103b** with sodium borohydride and acetic anhydride.[19]

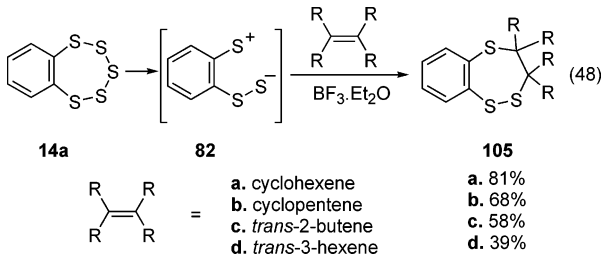
As seen above, when the trithiolobenzenepentathiepins **98c**,**d** are treated with sodium borohydride, it is the seven- rather than five-membered heterocyclic ring which is reduced more readily; indeed, with care it is possible to reduce **98c** to the bis-trithiole **17** in good yield.[9]



Exhaustive reaction of pentathiepin **64** with Raney nickel in boiling THF gave the fully desulfurized (unstable) benzofulvene **104**.[27]

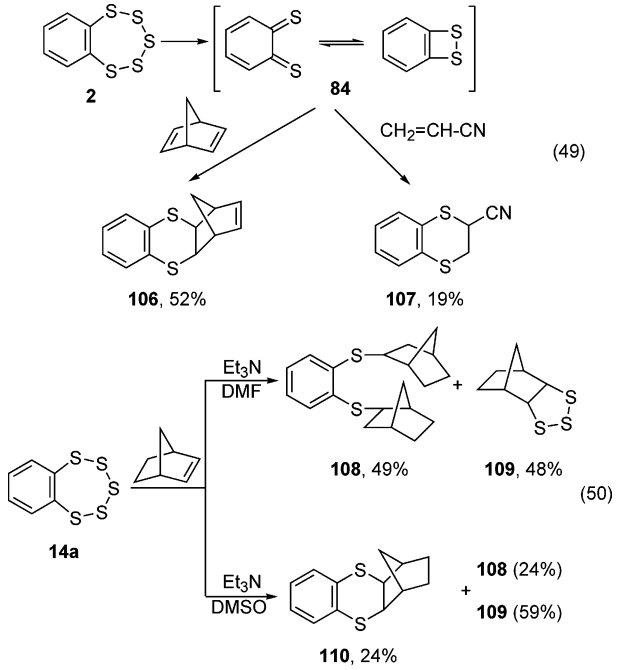
3.4. Reactions with Alkenes, Alkynes, and Arenes

Benzopentathiepin **14a** reacts with simple alkenes in the presence of a Lewis acid or triethylamine. When catalyzed by boron trifluoride etherate, the unsymmetrical 1,2,5-benzotrithiepins **105** were formed where the pentathiepin has reacted as a 1,5-dipole equivalent **82** (cf. Scheme 1).[41] Other Lewis acids were less effective than boron trifluoride. In the presence of triethylamine in DMF, the reaction took a different course with the loss of three sulfur atoms to give 1,4-dithianes **106** and **107**.[35]

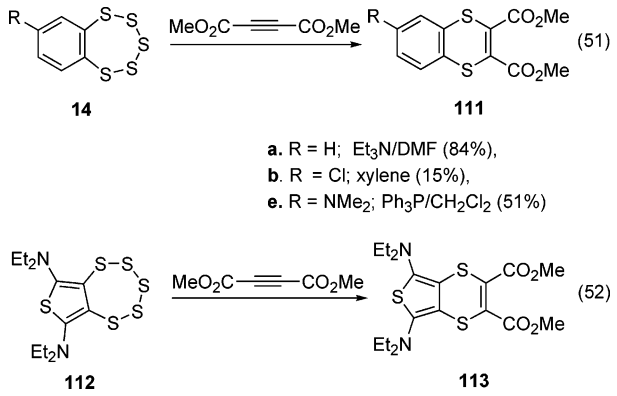


However, with norbornene and the amine in DMF, the trisulfur−norbornene cycloadduct **109** was formed, together with the 2:1−adduct **108**. The same reaction in DMSO also gave **108** and **109** together with the dithiane **110**.

Benzopentathiepins **14a**,**b**,**e** react slowly with DMAD to give the benzodithiins **111** only; the reaction is greatly accelerated by the addition of triphenylphosphine.[11,35] The pentathiepin **112** reacts with DMAD and triphenylphosphine in DCM at room temperature to give the 1,4-dithiin **113** in 78% yield.[29] Triphenylphosphine presumably initiates reaction by nucleophilic attack on sulfur, opening the pentathiepin ring and removing sulfur atoms, possibly to give



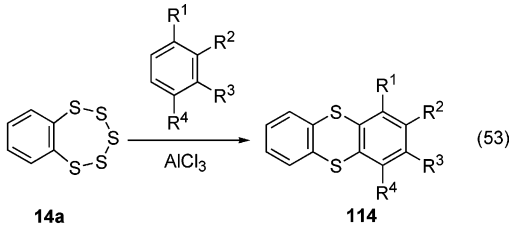
intermediate **84** (Scheme 1),[35] which is intercepted by DMAD (see also the reactions of Grignard reagents in section 3.6 below).



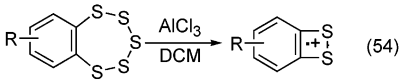
In a similar Lewis acid ($AlCl_3$) catalyzed reaction, benzopentathiepin reacted with benzene and some fused derivatives to give the corresponding thianthrenes **114**, often in high yields.[42] Pentathiepins **115** were converted by $AlCl_3$ in DCM into the radical cation **116**, which could be implicated in these Friedel−Crafts-type reactions.[43]

3.5. Reactions with Active Methylene Compounds

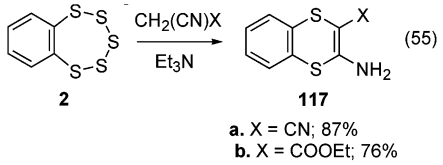
Various active methylene compounds such as malononitrile, ethyl cyanoacetate, ethyl acetoacetate, acetylacetone, and ethyl 2-chloropropionate react with benzopentathiepin **2** in the presence of triethylamine or sodium ethoxide to give 1,4-dithiins, 1,3-dithiols, and, less commonly, 1,2,4-trithiins.[44] Malononitrile and ethyl cyanoacetate gave the dithiins **117** in high yield. Ethyl acetoacetate and acetylacetone gave the benzodithiole **118** with triethylamine and the benzodithioles **119** with sodium ethoxide. Dithioles **118** (40%) and **119a** (42%) were also produced from **2** and ethyl 2-chloroacetoacetate. With ethyl 2-chloropropionate and sodium ethoxide,

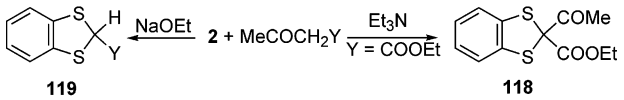


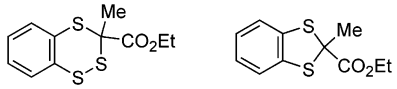
114 **a.** $R^1 = R^2 = R^3 = R^4 = H$; 44%
b. $R^1 = R^4 = Me$, $R^2 = R^3 = H$; 75%
c. $R^1 = R^4 = Pr^i$, $R^2 = R^3 = H$; 62%
d. $R^1 = R^2 = R^3 = R^4 = Me$; 83%
e. $R^3 = R^4 = H$, $R^1, R^2 =$ 93%
f. $R^1 = R^4 = Me$, $R^2, R^3 =$ 20%
g. $R^1 = R^2 = H$, $R^3, R^4 =$ 43%
$R^1 = R^2 = H$, $R^3, R^4 =$ 43%



however, the main product was trithiin **120** together with the dithiole **121**. These transformations were all rationalized by considering **2** to be reacting as the equivalent of the species **82**, **84**, and **85** in Scheme 1.



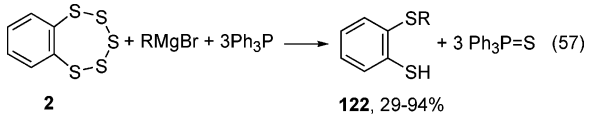




3.6. Reactions with Grignard Reagents

Sato and co-workers showed that benzopentathiepin **2** reacts with alkyl and aryl Grignard reagents in the presence of triphenylphosphine in ether at room temperature to give 2-alkylthio- and 2-arylthiobenzenethiols **122**, providing a useful synthesis of these compounds. In the absence of triphenylphosphine, the reactions were complex and much lower yielding.[45] A plausible reaction mechanism could again involve the removal of three sulfur atoms from **2** by the phosphine to give the intermediate **84**, which

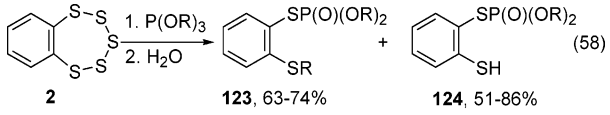
is intercepted by the Grignard reagents to give the observed products.



2 **122**, 29-94%

3.7. Reactions with Phosphorus Reagents

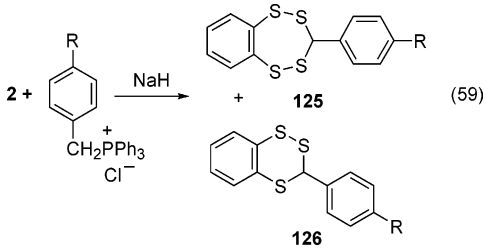
As mentioned above, the reactions of benzopentathiepins with DMAD and Grignard reagents are catalyzed by triphenylphosphine. Benzopentathiepin **2** reacted with trialkyl phosphites to give thiophosphonates **123** and **124**, mostly in good yields; the former were obtained selectively at −15 °C and the latter at reflux in DCM.[46] These products could arise by similar interception of intermediate **84** by the trialkyl phosphite.



2 **123**, 63-74% **124**, 51-86%

R = Me, Et, Pr^i, Bu, Ph

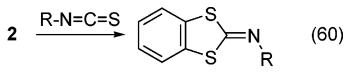
Pentathiepin **2** suffered milder degradation by nucleophilic attack on sulfur by the ylidic carbon when treated with benzylic phosphonium salts and sodium hydride to give mixtures of the tetrathiepins **125** and trithiins **126** in moderately good yields.[47]



	125	126
a. R = H	15%	52%
b. R = NO_2	0%	55%
c. R = Me	19%	51%
d. R = OMe	45%	25%
e. R = Cl	7%	53%

3.8. Reactions with Isothiocyanates

2-Imino-1,3-benzodithioles **127** were prepared, mostly in very good yield, from **2** and isothiocyanates in the presence of triethylamine.[48] The aryl isothiocyanates react faster than the alkyl compounds, and their reactions are accelerated by electron-withdrawing groups. Phenyl isocyanates did not react with **2**, but phenyl isoselenocyanate gave the same product, **127d**, as phenyl isothiocyanate. The analogous reaction with isocyanides, possibly to give the same products, has not yet been reported.

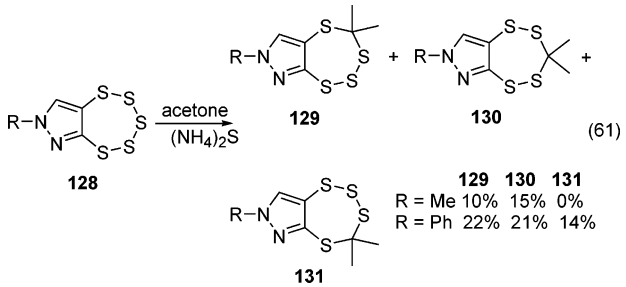


127

a. R = Me; 81% **e.** 4-MeC_6H_4; 77%
b. R = Et; 59% **f.** 4-ClC_6H_4; 84%
c. R = Pr; 47% **g.** 4-$MeOC_6H_4$; 74%
d. R = Ph; 78% **h.** 2-$MeOC_6H_4$; 86%

3.9. Reactions with Acetone

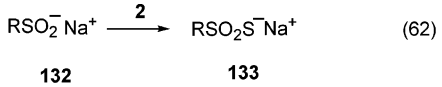
The two pyrazolopentathiepins **128** reacted with acetone and ammonium sulfide at room temperature to give the tetrathiepins **129**−**131** in the yields shown.[49] The structures, energetics, and conformational dynamics of these tetrathiepins were examined in detail, but the mechanism and scope of this ready reaction have not been reported. Presumably the pentathiepine ring is opened by sulfide ion attacking the three sulfur atoms bonded only to sulfur to give, with loss of S_2, bis-nucleophilic intermediates analogous to **80** and **81** in Scheme 1, which condense with acetone.



	129	130	131
R = Me	10%	15%	0%
R = Ph	22%	21%	14%

3.10. Miscellaneous Reactions of Pentathiepins

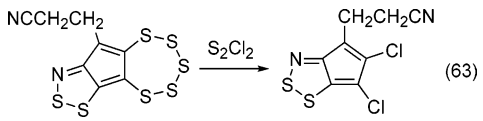
Not surprisingly, pentathiepins can act as sulfur transfer reagents to other substrates. Thus, sodium alkane- and arene-sulfinates **132** are readily converted into thiosulfonates **133** by benzopentathiepin **2** in high yields at room temperature.[50]



132 **133**

R = Me (78%), Ph (99%), $PhCH_2$(81%), $PhCH_2CH_2$ (86%), $Cl(CH_2)_4$ (78%), 4-MeC_6H_4 (100%), 4-ClC_6H_4 (82%), 4-$MeOC_6H_4$ (96%), 4-BrC_6H_4(85%), $EtO_2CCH_2CH_2$ (69%)

Loss of all five sulfur atoms from a pentathiepin was unexpectedly observed when **49** was treated with an excess of disulfur dichloride for a few days at 4 °C to give the dichloro compound **47**. Marked electron release from the two dithiazole sulfurs in **49** to the chlorinated carbon positions may possibly facilitate this unusual reaction by activating the pentathiepin carbons to *ipso* chlorination by S_2Cl_2.[21]



49 **47**

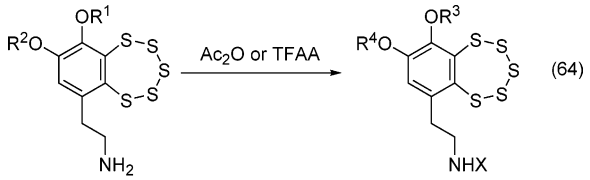
4. Reactivity of Substituents on Pentathiepin-Fused Rings

These reactions, largely of substituted benzopentathiepins, are significant in the present context in

showing the stability of the polysulfur ring toward a variety of reaction conditions.

4.1. Reactions of Amino and Hydroxy Groups

Since the pentathiepin ring is susceptible to nucleophilic attack,[6] protection of side-chain amino groups by acylation is stabilizing. *N*-Acetylation and trifluoroacetylation have been reported with acetic[40,51] and trifluoroacetic[19,52] anhydride; acetic anhydride also acetylated phenolic groups (eq 64).

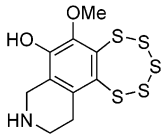


(64)

134 **135**

a. R^1 = Me, R^2 = H
b. R^1 = H, R^2 = Me
c. R^1 = R^2 = Me

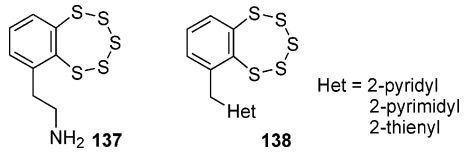
a. R^3 = Me, R^4 = X = Ac
b. R^4 = Me, R^3 = X = Ac
c. R^3 = R^4 = Me, X = $COCF_3$
d. R^3 = Me, R^4 = H, X = $COCF_3$
e. R^3 = H, R^4 = Me, X = $COCF_3$



136

Lissoclinotoxin B **136** was similarly acetylated on nitrogen and oxygen in pyridine at room temperature.[19] The pentathiepin ring in varacin **3** is also stabilized by converting the side-chain amino group into a urea by reaction with the (*S*)-(+)-1-(1-naphthylethyl)isocyanate.[53]

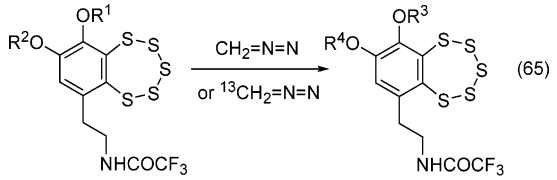
The free base **137** once liberated from its hydrochloride is very sensitive, but the free bases **138**, with less nucleophilic side chains, are all stable (Figure 2).[6]



137 **138**

Figure 2.

Methylation of the phenolic groups in **139** with diazomethane and ^{13}C diazomethane, used in the structure determination of lissoclinotoxin A, left the pentathiepin ring intact.[52]



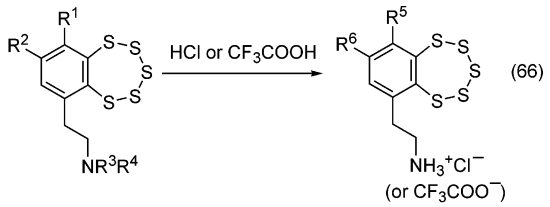
(65)

139 **140**

R^1 = H, R^2 = Me
R^1 = Me, R^2 = H

a. R^3 = R^4 = Me
b. R^3 = Me, R^4 = $^{13}CH_3$
c. R^3 = $^{13}CH_3$, R^4 = Me

The substituted amino groups were deprotected with hydrochloric and trifluoroacetic acid to give stable amine salts of varacin and lissoclinotoxin A (eq 66).[6,8,19,20]

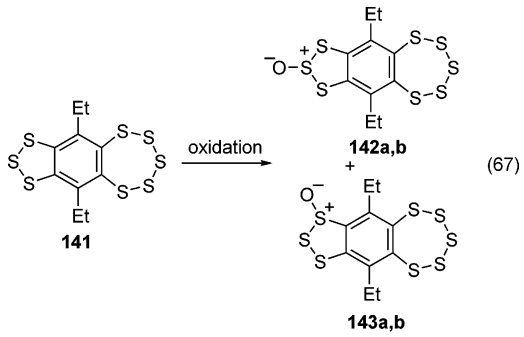


(66)

a. R^1 = R^2 = R^5 = R^6= OMe, R^3 = H, R^4 = $CO_2(CH_2)_2SiMe_3$ (CF_3COOH) 86%
b. R^1 = R^2 = R^5 = R^6= OMe, R^3 = CHO, R^4 = Boc (HCl) 46%
c. R^1 = R^2 = R^5 = R^6= OMe, R^3 = H, R^4 = Boc (CF_3COOH) 100%
d. R^1 = R^2 = R^5 = R^6= R^3 = H, R^4 = Boc (HCl) 96%
e. R^1 = OCH_2OMe, R^2 = R^6 = OMe, R^3 = H, R^4 = $CO_2(CH_2)_2SiMe_3$, R^5 = OH (CF_3COOH) 94%

4.2. Oxidation and Reduction of Fused Trithiole Rings

The tricyclic compounds **141** (Figure 3) and **16a** have both fused trithiole and pentathiepin rings. The

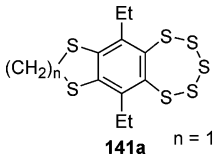


(67)

141 **142a,b** **143a,b**

1. mcpba: **142a**, 16%; **142b**, 13%; **143a**, 26%; **143b**, 32%
2. *t*-BuOOH: **142a** + **142b**, 29%; **143a**, 18%; **143b**, 23%

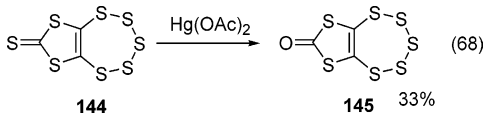
former was oxidized with MCPBA[54] or with $Ti(OPr^i)_4$/*R*,*R*-DET/t-BuOOH.[55a] In each case the trithiole ring, but not the pentathiepin ring, was oxidized, four monoxides **142a**,**b** and **143a**,**b** being isolated. **142a**,**b** are nonchiral conformational isomers with a plane of symmetry, while the unsymmetrical **143a**,**b** are diastereoisomers with respect to the pentathiepin ring and the configuration of the sulfinyl group (see also section 5.7). When the closely related compounds **141a** were oxidized with the same reagents, the smaller heterocyclic ring was again oxidized preferentially, but this was now accompanied by desulfurization and contraction of the pentathiepin ring to a trithiole.[55b]



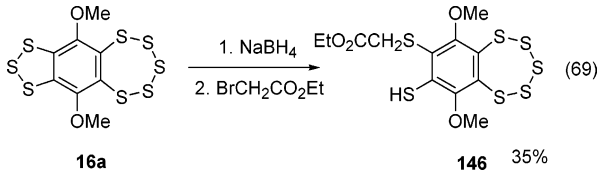
141a n = 1,2

Figure 3.

The pentathiepin ring also survives oxidation by mercuric acetate in the conversion of the fused 1,3-dithiolo-2-thione **144** into the corresponding keto compound **145**.[56]

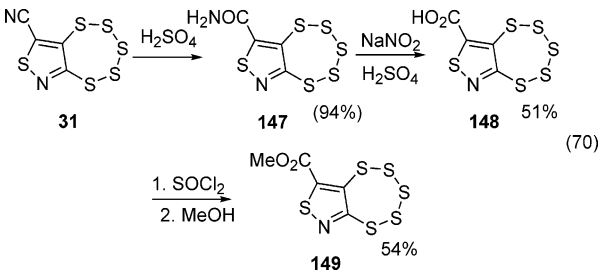


Although it is known that $NaBH_4$ reduces the pentathiepin ring (section 3.3), when the trithiolobenzopentathiepin **16a** was treated with a deficiency of $NaBH_4$, the trithiole ring was reduced preferentially, followed by alkylation to give **146** in modest yield.[7]



4.3. Reactions of Carboxylic Acid and Related Groups

One of the earliest pentathiepins to be well characterized and studied was the cyanoisothiazolo compound **31**, where the high stability of the polysulfur ring toward acid was established. The cyano group was hydrated to the amide **147** in cold concentrated sulfuric acid in very high yield. The amide was converted to the acid **148** with sodium nitrite and concentrated sulfuric acid, and this, with thionyl chloride followed by methanol, gave the methyl ester **149** (eq 70).[11]



5. Physical and Theoretical Properties

5.1. UV and IR Spectroscopy

UV spectra vary significantly with the structure of the pentathiepin; there is little obvious relationship between the character of the UV bands and the molecular structure. For unsubstituted pentathiepin **1**, there are weak shoulders at 206 nm (ϵ = 9730), 253 (3440), and 315 (1510).[1] For most benzopentathiepins there is only one common band at about 210 nm (ϵ = 25000−32000).[1,11,40,52] Benzopentathiepins condensed with a trithiolo ring, **18** (eq 6) and **141** (eq 67), have a different band at 292−294 nm (ϵ = 15100−15500).[57] Pentathiepins condensed with pyrrole, pyrazole, or thiophene have λ_{max} at 230−240 nm.[11,24]

There are S−S absorption bands in the IR spectra of pentathiepins at 460−485 cm^{-1}.[58]

5.2. Raman Spectroscopy

Throughout the series of benzo- and pyrazolopentathiepins there is strong absorption in the region 485 cm^{-1}.[11] There is often a two-band absorption with the higher one (490 ± 5 cm^{-1}) always being the stronger. Benzopentathiepins have two additional characteristic absorptions at 425 ± 5 cm^{-1} (weak to medium) and 180 ± 5 cm^{-1} (strong) which may be useful in the identification of benzopentathiepins.

5.3. NMR Spectroscopy

The ring protons of pentathiepin **1** appear at δ 7.42 ppm and of benzopentathiepin as an AA′BB′ system centered at δ 7.52 ppm.[1] The ring carbons of pentathiepins appear at low field (δ 135−145 ppm);[15,19,36,39,56,59] when the carbon is also bonded to nitrogen, as in the isothiazolopentathiepin **31**, its signal appears at δ 170.1.[15]

5.4. Mass Spectrometry

Mass spectrometry is important for establishing the pentathiepin structure, electron ionization being mostly used. In practically all cases the intensity of the molecular ion is low (0.6−25%), with major fragmentation being a characteristic loss of S_2 (40−100%), not S_1.[24,25,31,36,40,56,60,61] FAB mass spectrometry has been used,[51,52] but it is not yet clear whether this is any better for pentathiepin identification.

5.5. X-ray Diffraction

The molecular structures of more than 20 pentathiepins have been determined by X-ray diffraction. All the pentathiepin rings have chairlike conformations (see below). The S−S bond lengths vary from 2.039 Å in benzopentathiepin **2**[62] to 2.063 Å in dithiolopentathiepin **144**[63] but are still close to the S−S bond length in S_6 (2.057 Å) and S_8 (2.051 Å). The S−S−S bond angles and S−S−S−S torsional angles are also close to the corresponding values in S_6 and S_8. The S−C bond length in pentathiepins (1.744−1.795 Å) compare with S−C (sp^2) single bonds (1.78 Å).[11,63,64]

5.6. Electrochemistry

The electrochemical properties of the pentathiepin **36** (Figure 4) were investigated by cyclic voltammetry, and two pairs of reversible redox waves were observed at +0.69 and +1.06 V; these are higher than those of BEDT−TTF (+0.53 and +0.89 V) under identical conditions.[17] This suggests that the electron-donating ability of **36** is lower than that of BEDT−TTF, possibly owing to the inductive effect of its extra sulfur atoms.

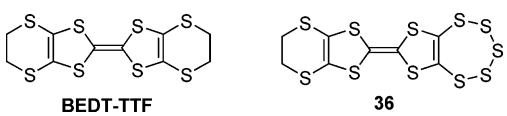


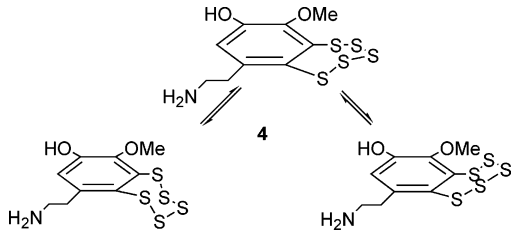
Figure 4.

5.7. Conformation and Chirality

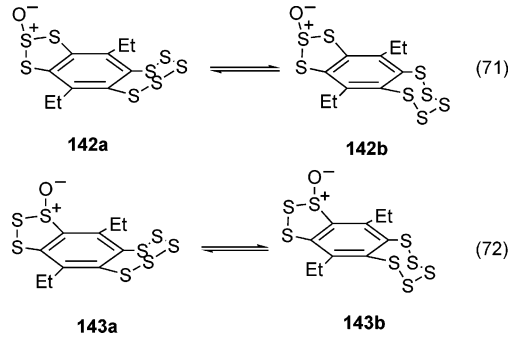
The ^1H NMR spectra of varacin **3** and lissoclinotoxin A **4** showed unexpectedly complex signals for the side-chain benzylic protons.[52,53] This signal complexity is the result of a high energy barrier (ca. 30 kcal·mol^{-1}) for inversion of the pentathiepin ring,

which induces asymmetry in the molecule, making the protons diastereotopic. An increase in temperature from 25 to 100 °C caused the signals to sharpen, and distinctly diastereotopic signals were observed. The cause of the high energy barrier lies, presumably, in unfavorable eclipsing of sulfur lone pair orbitals on passing through the half-chair transition state during ring inversion (Scheme 2).[52]

Scheme 2. Inversion of the Pentatiepin Ring in Lissoclinotoxin A



Four monoxides **142a**,**b** and **143a**,**b** were formed by oxidation of the trithiolobenzopentathiepin with MCPBA, and their structures were determined by X-ray crystallography.[54] The pair of 1-oxides (eq 72) and the pair of 2-oxides (eq 71) interconverted slowly in chloroform at room temperature by inversion of the pentathiepin rings for which the activation parameters were determined; $^{298}\Delta G^{\ddagger}$ was close to 24 kcal mol^{-1} in each case (see also section 4.2).[55]



(71)

(72)

5.8. Calculations

The conformations of pentathiepin **1**, benzopentathiepin **2,** and thienopentathiepin **55** (eq 21) were studied by the semiempirical AMI method.[65] The rather rigid chair forms were found to be the most stable. CNDO calculations of the UV spectra accounted well for the main absorption bands.

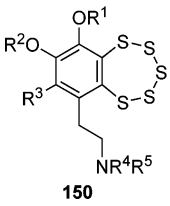
Excellent agreement was found between experiment and ab initio molecular orbital calculations (SCF and MP-2 level) for the structure and conformational behavior of benzopentathiepin **2**; the chair conformation was more stable than the twist-boat and boat conformations.[49] PM3 calculations of the HOMO and LUMO for **2** support initial nucleophilic attack by trialkyl phosphites on sulfur at position 2, leading to the products **123** and **124** described earlier (see section 3.7).[46]

Pentathiepin structures and reactions have recently been studied in detail by density functional theoretical (DFT) calculations, and a detailed discussion is given by Greer.[66a] These calculations accurately reproduce the experimental structure and conformations of pentathiepins, and a detailed discussions in given by Greer. Most interestingly and unexpectedly, the decomposition of pentathiepin **1** (nucleophilic attack by SH^-) appears to be triggered by attack at S_1 rather than S_2 to generate a delocalized enethiolate anion, followed by the extrusion of S_3 rather than the ubiquitous S_2. This novel generation of the as yet undetected S_3 is considered to be an important factor in the chemistry and particularly the biochemistry of pentathiepins; it is proposed, for example, to have significance in the mechanism of cytotoxicity of varacin **3**. This generation of S_3 has now been coupled with the role of the aminoalkyl side chains found in all biologically active, naturally occurring pentathiepins to date. The key process is intramolecular nucleophilic attack by primary and secondary, but not tertiary, amino group at S(1) of the fused pentathiepin ring to generate the reactive S_3 intermediate. Trapping of S_3 with norbornene and dimethylbutadiene is described, though the products formed are characteristic of the well-established species S_2.[66b]

As noted earlier (section 3), the dominant pathway for decomposition of the polysulfur ring in the chemistry of pentathiepins is the overall loss of three of the sulfur atoms. This could, of course, simply be the consequence of breaking S−S but not C−S bonds, possibly to give the stabilized intermediate **84** shown in Scheme 1.

6. Biological Activity and Applications

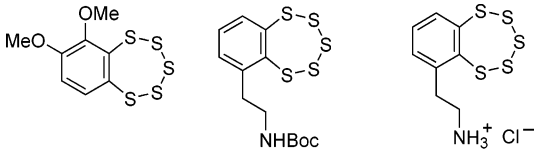
The first naturally occurring pentathiepin, varacin **150a** (Figure 5), was isolated from the marine ascidian *Lissoclinum vareau* in 1991.[38] A few other closely related pentathiepins were isolated in the following few years: lissoclinotoxin A **150b** from ascidian *Lissoclinum* sp.,[52] lissoclinotoxin B **150c** from tunicate *Lissoclinum perforatum*,[40] *N*,*N*-dimethyl-5-(methylthio)varacin **150d** from the Palauan ascidian *Lissoclinum japonicum*, 5-(methylthio)varacin **150e** in an inseparable 2:3 mixture with the corresponding trithiole from a different *Lissoclinum* species from Pohnpei, and 3,4-desmethylvaracin (**150f**) from a *Eudistoma* sp. from Pohnpei.[39]



a. $R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$
b. $R^1 = Me$, $R^2 = R^3 = R^4 = R^5 = H$
c. $R^1 = Me$, $R^2 = R^5 = H$, R^3, $R^4 = -CH_2-$
d. $R^1 = R^2 = R^4 = R^5 = Me$, $R^3 = SMe$
e. $R^1 = R^2 = Me$, $R^3 = SMe$, $R^4 = R^5 = H$
f. $R^1 = R^2 = R^3 = R^4 = R^5 = H$

Figure 5.

Various synthetic and natural pentathiepins are biologically active. Varacin exhibits cytotoxicity toward the human colon cancer HCT 116 with an $IC_{90} = 0.05\ \mu g/mL$, 100 times the activity of 5-fluorouracil in this assay, and a 1.5 differential toxicity toward the CHO cell line EM9 (chlorodeoxyuridine sensitive) versus BR1 (BCNU resistant), providing the first evidence that varacin damages DNA.[38] *N*,*N*-Dimethyl-5-(methylthio)varacin **150d** and the synthetic benzopentathiepins **7g**, **7h**, and **151** (Figure 6) ex-



7g 7h 151

Figure 6.

hibit cytotoxicity with IC_{50} = 6.1, 3.2, and 0.26 μg/mL, respectively, toward HeLa53 cells. Pentathiepin **151** is 10 times more cytotoxic than the corresponding *ortho*-dithiol from which it was made.[5]

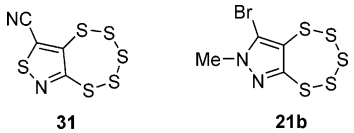
7-Methylbenzopentathiepin, lacking the aminoethyl group of the natural products, has thiol-dependent DNA-cleaving ability; this provided the first direct evidence that pentathiepins can cleave DNA under physiological conditions.[67a] It has now been shown that thiols degrade the heterocyclic ring of 7-methylbenzopentathiepin extensively by the usual nucleophilic attack, faster than in the analogous reactions with di- and trisulfides; this lends support to the likely biological significance of natural pentathiepin cytotoxins reacting with endogenous cellular thiols.[67b]

It has now been shown that varacin is highly efficient at DNA cleavage in the presence, but not in the absence, of a thiol (2-mercaptoethanol) and that this activity is enhanced by an increase in the concentration of the thiol and a decrease in the pH. The high cytotoxicity of varacin was also demonstrated for several cancer cell lines, the IC_{50} ranging from about 1 to 50 nM.[68]

All natural benzopentathiepins so far isolated have an aminoethyl substituent. The positively charged amino substituent may confer DNA affinity on the pentathiepin antibiotics.[67] 3,4-Desmethylvaracin (**150f**) and *N*,*N*-dimethyl-5-(methylthio)varacin **150d** selectively inhibit protein kinase C with IC_{50} ca. 1 μg/mL.[39]

Lissoclinotoxin A **150b** and B **150c** are powerful antimicrobial agents; **150b** exhibited activity similar to that of cefotaxim against a range of organisms.[40] Both **150b** and **150c** were about as active against ichthyopathogenic strains as ampicillin.

Varacin **150a**, lissoclinotoxin A **150b**, and benzopentathiepin **2** exhibit potent activity in vitro against *Candida albicans* and *Bacillus subtilus*.[38,51,52] The results for **2** show that this activity in the benzopentathiepin series does not depend on the presence of the side-chain amino group. Fungicidal activity of pyrazolopentathiepin **31** has been patented (Figure 7);[69−72] it controlled *Phytophthora infestans* in tomatoes[73] and *Venturia inaecqualis* infection in apples.[74] 7-Trifluoromethylbenzopentathiepin gave 100% control of apple scab virus, and the 7-dimethylamino analogue gave 100% control of cucumber mosaic virus.[75] Pyrazolopentathiepin **21b** gave 100%, 80%, and 77% control, respectively, of apple scab, wheat rust, and bean *Botrytis*.[76] Trithiolobenzopentathiepin



31 21b

Figure 7.

141 (eq 67) was proposed for promotion of fruit body formation of mushrooms.[77]

Pentathiepins obtained from the reaction of norbornene and its derivatives with sulfur were proposed as vulcanization accelerators for diene rubber.[78] Benzo- and cyclohexapentathiepin were used as additives in the emulsion layers and/or adjacent hydrophilic colloid layers as antifogging agents in photography;[79] pentathiepins have also been claimed to improve the properties of other photographic materials.[80−85]

7. Conclusions

It is apparent from this account that the well-known catenation of sulfur atoms to form medium to large polysulfur rings can survive the introduction of a carbon−carbon double bond into the ring. Only the five-membered trithioles and the seven-membered pentathiepins have been reasonably well explored so far, and these are most commonly fused to other ring systems, notably benzenes. The pentathiepins are usually the most stable of these C_2S_n rings, being the thermodynamic products of many of the cyclization reactions described here. Since their first laboratory preparation in 1971 and their discovery in natural products in 1991, these novel compounds have aroused much interest, partly because of their striking stability, the high energy barrier (up to ca. 30 kcal mol^{-1}) for inversion of the chairlike C_2S_5 ring, and its somewhat surprising occurrence in antibiotics, some of which have potent biological activity.

Pentathiepin rings can be readily constructed in rational ways, but they also appear as products of some puzzling reactions. Because of the many possibilities for nucleophilic or electrophilic attack at the five sulfur atoms, these heterocycles display a diverse range of chemical reactions, some obvious and some much less so. Only one or two examples are known for many of these reactions, the scope and mechanism of which are in need of clarification.

8. Acknowledgments

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