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1,2,3,4,5-Pentathiepines and 1,2,3,4,5-pentathiepanes

L S Konstantinova, S A Amelichev, O A Rakitin

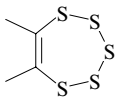
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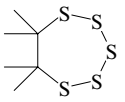
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Abstract. Data on the synthesis and properties of seven-membered heterocyclic compounds containing five successive sulfur atoms and a carbon – carbon bond, 1,2,3,4,5-pentathiepines and -pentathiepanes, are generalised and described systematically. The bibliography includes 104 references.

I. Introduction

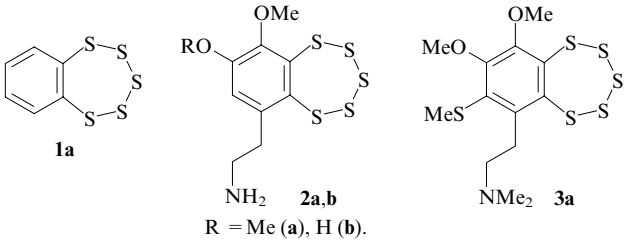
Among seven-membered polysulfur-containing heterocycles containing five sulfur atoms and two carbon atoms, there are 1,2,3,4,5-pentathiepines and -pentathiepanes and 1,2,3,4,6- and 1,2,3,5,6-pentathiepanes. Data on the two last-mentioned classes of compounds, whose properties are substantially different from those of 1,2,3,4,5-isomers, are beyond the scope of the present review. We review data on methods for the synthesis and reactions of seven-membered rings, which contain a carbon – carbon double or single bond and a chain of five sulfur atoms, *viz*., 1,2,3,4,5-pentathiepines and their hydrogenated analogues, 1,2,3,4,5-pentathiepanes.





Fehér was the first to synthesise such derivatives: pentathiepanes in 1967 (Ref. 1) and pentathiepines in 1971.[2] Twenty years later, a seven-membered polysulfur-containing ring was found in natural antibiotics isolated from marine organisms (cited in Ref. 3). In recent years, pentathiepines have attracted considerable interest as antitumour, antifungal and antiseptic drugs. Apparently, it is the heterocycle that is responsible for their biological activity. In addition, 1,2,3,4,5-pentathiepines have found application in industry, for example, as cathodic materials. These compounds are also valuable starting compounds in synthetic organic chemistry, because they can be used for the preparation of various sulfur-containing derivatives, both cyclic (1,4-dithiines, 1,2,4,5-tetrathiocines and 1,3-dithioles) and acyclic (vicinal 1,2-dithiols and many other compounds).

Among natural and synthetic pentathiepines, benzopentathiepine (**1a**) and its analogues containing a substituted benzene ring are best studied. Natural compounds, such as varacin (**2a**), lissoclinotoxin A (**2b**) and *N,N*-dimethyl-5-(methylthio)-varacin (**3a**), have antiseptic and antifungal activities and inhibit protein kinase C. In addition, varacin exhibits antitumour activity.



1a **2a**,**b** **3a**

R = Me (**a**), H (**b**).

In 2004, we published a review[3] on the chemistry of pentathiepines. Data on reviews on pentathiepanes are lacking in abstract journals, although data on both classes of compounds were included in chapters of the monograph *Comprehensive Heterocyclic Chemistry*.[4] In the present review, the results of research into the chemistry of 1,2,3,4,5-pentathiepanes are analysed for the first time. Since the synthesis methods, chemical properties and spectroscopic characteristics of 1,2,3,4,5-pentathiepines and their hydrogenated analogues are rather similar, it is worthwhile to consider and compare data on these heterocycles in one paper, with a supplement of studies on pentathiepines published in the last three years.

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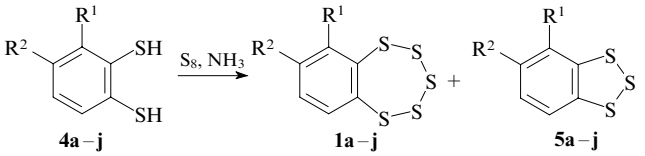
II. Methods of synthesis

1. Sulfurisation of sulfur-containing compounds by elemental sulfur

a. Synthesis of pentathiepines from aromatic vicinal dithiols

Benzopentathiepine (**1a**) and its 7-chloro-substituted analogue (**1b**) were synthesised by Sato *et al*.[5] by the reaction of the corresponding arene-1,2-dithiols (**4a**,**b**) with elemental sulfur in liquid ammonia. The reactions were performed in a titanium

autoclave at 20 °C. More recently, this method was improved (for example, dichloromethane was used as the solvent), and a wide range of monosubstituted benzopentathiepines **1c–j** were synthesised.[6–8] In addition to thermodynamically stable pentathiepines **1a–j**, sulfurisation of arene-1,2-thiols with elemental sulfur affords less stable benzo-1,2,3-trithioles **5a–j** as by-products. Unfortunately, the yields of the reaction products were not reported in the cited studies.

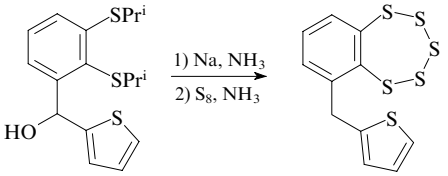


R^1 = H: R^2 = H (**a**), Cl (**b**); R^2 = H: R^1 = $SiMe_3$ (**c**), $SiMe_2Bu^t$ (**d**), $SiEt_3$ (**e**), $SiPh_3$ (**f**), $CH_2CH_2NH_2$ (**g**), CH_2CH_2NHBoc (**h**), CH_2Py (**i**), CH_2Pyrm (**j**)

Boc is *tert*-butoxycarbonyl, Py is 2-pyridyl, Pyrm is 2-pyrimidyl.

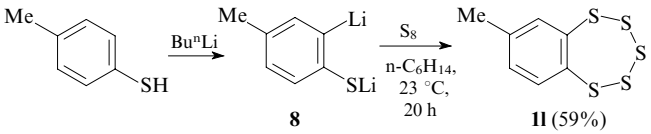
This method was used for the synthesis of 6-(2-aminoethyl)benzopentathiepine (**1g**) and 6,7-dimethoxybenzopentathiepine (**6a**) as structural analogues of the natural antibiotic varacin (**2a**).[7]

The reaction can be performed with *S*,*S*-dialkyl-substituted arene-1,2-dithiols instead of thioles. In this case, the pentathiepine ring is synthesised in two steps. Compound **7** is dealkylated by sodium in liquid ammonia, which is accompanied by reduction of the hydroxy group, and the subsequent reaction with sulfur produces pentathiepine **1k**.[8]



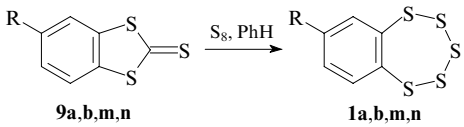
Recently, the synthesis of phthalocyanines fused with the pentathiepine ring by the reaction of the corresponding 4,5-(*o*-xylylenedithio)phthalonitrile derivatives with lithium amide and elemental sulfur has been documented.[9]

As an exception, let us mention the reaction ideologically similar to the above-considered method. In this reaction, aromatic monothiol was used as the starting compound. The treatment of dilithium intermediate **8**, which is generated *in situ* by the reaction of *p*-toluenethiol with butyllithium, with sulfur affords pentathiepine **1l**.[10]



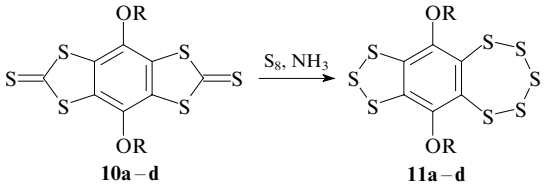
b. Synthesis from fused 1,3-dithiole-2-thiones

R Sato *et al.*[5] synthesised benzopentathiepine (**1a**) and its 7-monosubstituted analogues **1b**,**m**,**n** from fused 1,3-dithiole-2-thiones **9a**,**b**,**m**,**n** by the reaction with sulfur in liquid ammonia. The use of benzene as the solvent led to an increase in the yield of the reaction products. However, attempts to synthesise 7-nitrobenzopentathiepine according to this method failed. Interestingly, pentathiepine **1a** is derived from compound **9a** in higher yield compared to the reaction with benzene-1,2-dithiol (**4a**), although the latter is produced by hydrolysis of benzodithiole **9a** and is, presumably, an intermediate in the synthesis of pentathiepine **1a**.



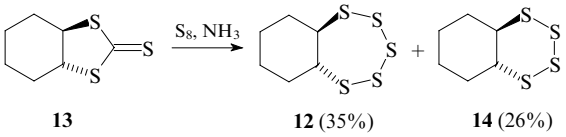
R = H (**a**, 82%), Cl (**b**, 59%), MeO (**m**, 99%), NH_2 (**n**, 91%).

The reaction of benzobis(dithiolethiones) **10a–d** with sulfur in liquid ammonia gives trithiolobenzopentathiepines **11a–d** in high yields rather than the corresponding benzobis(-pentathiepines).[11] Under these conditions, the reaction of benzobis(1,3-dithiole-2-thione) containing no alkoxy groups yields only polymers of unknown structure.



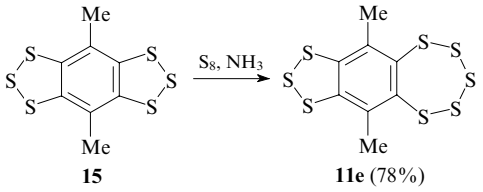
R = Me (**a**, 82%), Et (**b**, 99%), Pr^i (**c**, 99%), $PhCH_2$ (**d**, 62%).

Pentathiepane **12** fused with the cyclohexane ring was synthesised from 1,3-dithiole-2-thione **13** in low yield (35%) due to formation of tetrathiine **14** as a by-product.[12]



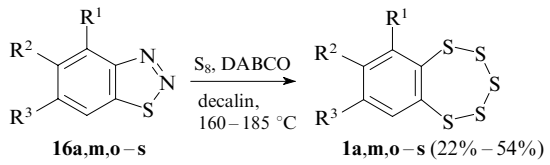
c. Synthesis from benzo-1,2,3-trithioles

Pentathiepines can be synthesised starting from benzo-1,2,3-trithioles. For example, the treatment of benzobis(trithiole) **15** with sulfur in liquid ammonia affords pentathiepine **11e** in good yield.[13]



d. Synthesis from annulated 1,2,3-thia(selena)diazoles

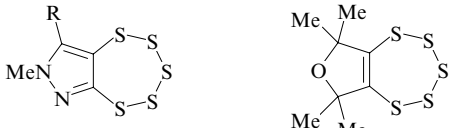
A procedure for the synthesis of benzopentathiepines from the corresponding 1,2,3-thiadiazoles was proposed and developed by Chenard *et al.*[14,15] The reaction proceeds upon heating (160–185 °C) of benzothiadiazoles **16a**,**m**,**o–s** with elemental sulfur in decalin. In the presence of diazabicyclo[2.2.2]octane (DABCO), final products **1a**,**m**,**o–s** were obtained in higher yields. The authors attributed this fact to high nucleophilicity of the organic base necessary for the S_8 ring opening. Benzothiadiazoles react as latent *o*-mercaptodiazonium salts. Apparently, the reaction initially leads to cleavage of the heterocycle in compound **16** accompanied by elimination of the nitrogen molecule and the resulting intermediate reacts with the activated [S_8–DABCO] species.



16a,m,o–s **1a,m,o–s** (22%–54%)

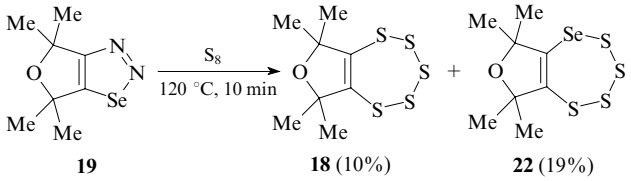
$R^1 = R^2 = R^3 = H$ (**a**); $R^2 = R^3 = H$: $R^1 = Br$ (**o**), CF_3 (**p**); $R^1 = R^3 = H$: $R^2 = OMe$ (**m**), NMe_2 (**q**); $R^1 = R^2 = H$: $R^3 = Cl$ (**r**), CF_3 (**s**).

This method allowed the synthesis of a series of pentathiepines annulated with heterocyclic rings, such as the pyrazole ring (**17**, 36%–44% yields)[15] or the dihydrofuran ring (**18**, 22%).[16]

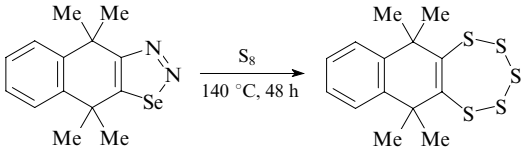


17: R = H, Br, CO_2Et **18**

Analogously, 1,2,3-selenadiazoles **19** and **20** are transformed into pentathiepines **18** and **21**, respectively. The reaction with compound **19** proceeds very rapidly to give predominantly 1-selena-2,3,4,5-tetrathiepine **22**.[17]



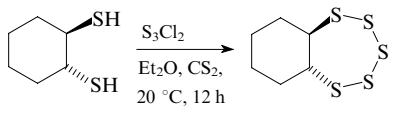
19 **18** (10%) **22** (19%)



20 **21** (25%)

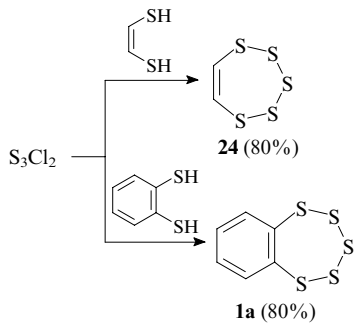
2. Sulfurisation of vicinal dithiols with other reagents

The first compound belonging to pentathiepanes, *viz*., perhydrobenzopentathiepane (**12**), was synthesised by Fehér and Degen [1] from *trans*-cyclohexane-1,2-dithiol (**23**) with the use of the rare reagent dichlorotrisulfane (S_3Cl_2). The reaction was carried out in a mixture of diethyl ether and carbon disulfide at room temperature.



23 **12** (75%)

The parent compound of pentathiepines, *viz*., unsubstituted pentathiepine (**24**), and benzopentathiepine (**1a**) were

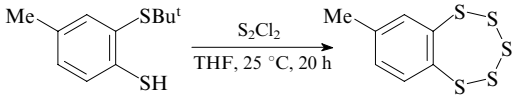


24 (80%)

1a (80%)

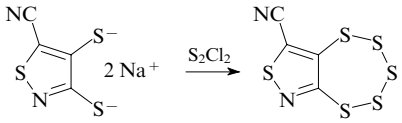
synthesised for the first time by the reaction of ethylene- and benzene-1,2-dithiols, respectively, with S_3Cl_2.[2]

More recently, this reaction was extended to other vicinal 1,2-dithiols. In these reactions, cheaper sulfur monochloride (S_2Cl_2) was used instead of S_3Cl_2. The limitations of this method are associated exclusively with stability and accessibility of the starting compounds. The reaction with sulfur monochloride can be performed also with mono-*S*-alkylated derivatives, for example, with compound **25**.[10] In this case, dealkylation occurs under mild conditions in the presence of a sulfur-containing reagent; the resulting benzothiepine **1l** was isolated by silica gel column chromatography.



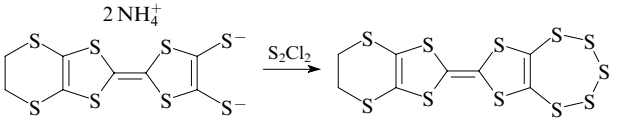
25 **1l** (86%)

The synthesis of annulated pentathiepines from salts, 1,2-dithiolates, was documented.[18–20] In particular, cyano-substituted pentathiepinoisothiazole **26** was synthesised from the corresponding disodium salt **27** in almost quantitative yield.[18]



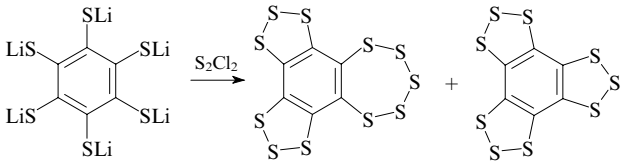
27 **26** (98%)

However, the analogous reaction with diammonium salt **28** produced pentathiepine **29** in substantially lower yield.[20]



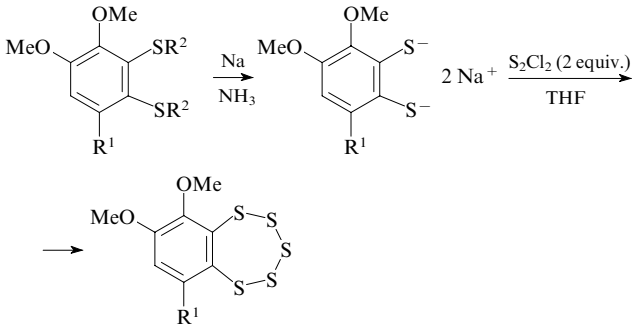
28 **29** (27%)

The reaction with the hexalithium salt of hexamercaptobenzene **30** afforded products in rather high total yield; however, pentathiepine **31** was obtained as a minor component of the mixture, and the reaction produced predominantly benzotris(trithiole) **32**.[19]



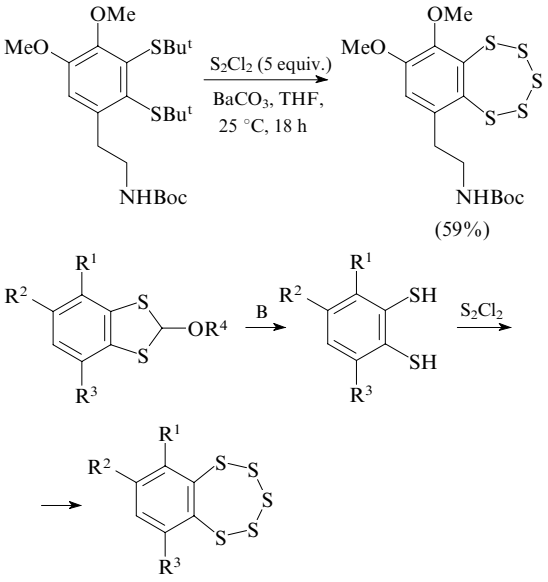
30 **31** (20%) **32** (74%)

It should be noted that vicinal dithiols can be generated *in situ* from various 1,2-bifunctional compounds.[10,15,21–26] Examples of reactions, in which intermediate dithiolate anions form the 1,2,3,4,5-pentathiepine ring, are given below. It

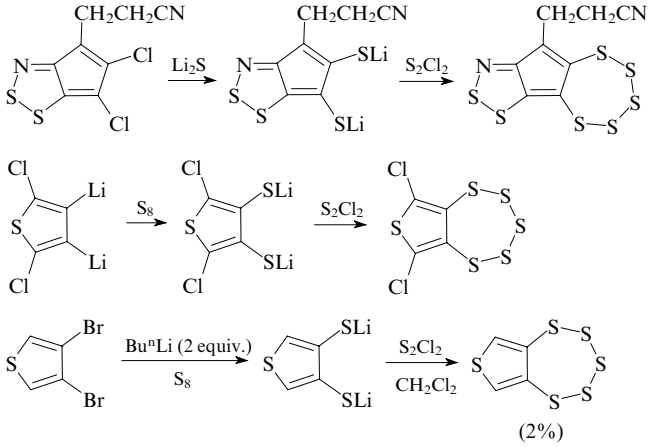


$R^1 = (CH_2)_2NHCO_2(CH_2)_2SiMe_3$; $R^2 = Pr^n$ (28%), Bu^n (47%).

should be noted that this reaction was described [10, 21–23] as one of steps in the total synthesis of natural pentathiepine analogues.



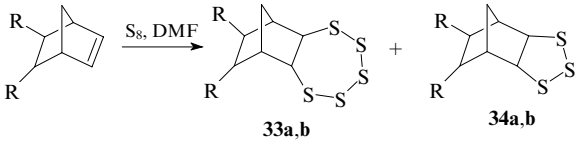
B is a base [Na, NH_3 (liq), *etc.*]; R^1 = H, Me; R^2 = R^3 = H, R^4 = Bu^n; R^1 = R^2 = OMe, R^3 = $(CH_2)_2NHBoc$, R^4 = iso-C_5H_{11}.



3. Cyclosulfurisation at a carbon–carbon multiple bond

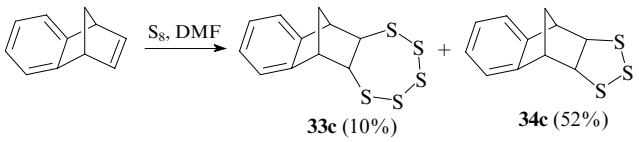
a. Reactions with elemental sulfur

One of the commonly used procedures for the synthesis of pentathiepanes is based on the reactions of cyclic and linear alkenes with elemental sulfur. However, this reaction generally gives products in low yields. For example, the reactions of norbornene derivatives with sulfur in DMF afford pentathiepanes **33a**–**c** in low yields, whereas the corresponding trithiolanes **34a**–**c** are obtained as the major products.[27]



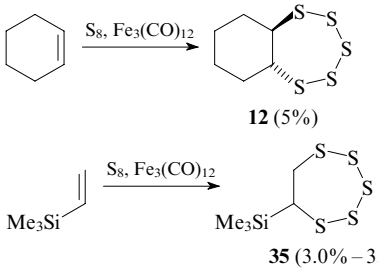
33a,**b** **34a**,**b**

Compound	R–R	Yield (%)	
		33	**34**
a	2 H	6.5	30
b	$CH_2CH{=}CH$	5	40



33c (10%) **34c** (52%)

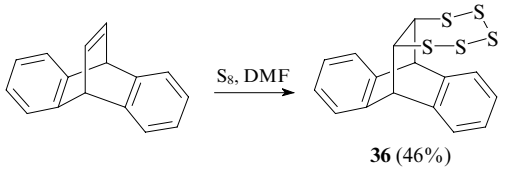
To stabilise intermediates, $Fe_3(CO)_{12}$ was added to the reaction mixture.[28,29] However, the use of this carbonyl as the catalyst for the reactions of cyclohexene [28] and vinyltrimethylsilane [29] with sulfur did not lead to an increase in the yield of pentathiepanes **12** and **35**.



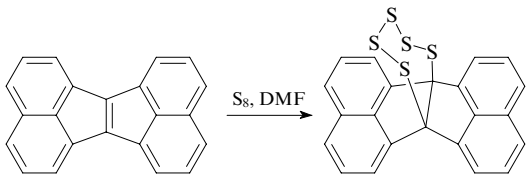
12 (5%)

35 (3.0%–3.7%)

The reactions with polycyclic aromatic alkenes produce fused pentathiepanes in considerably higher yields. For example, pentathiepanes **36** and **37** were synthesised by the reaction of barrelene [30] or acenaphtho[1,2-*a*]acenaphthylene [31] with elemental sulfur in DMF in 46% and 88% yields, respectively.

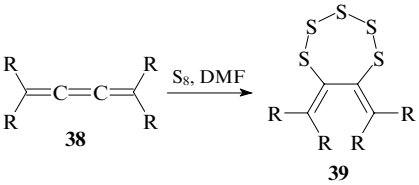


36 (46%)



37 (88%)

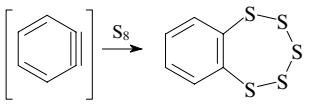
Due to steric hindrance, the analogous reaction of 1,1,4,4-tetrasubstituted buta-1,2,3-trienes **38** with sulfur proceeds regioselectively at the central C=C double bond to give compounds **39**, as a rule, in good yields.[17,32]



38 **39**

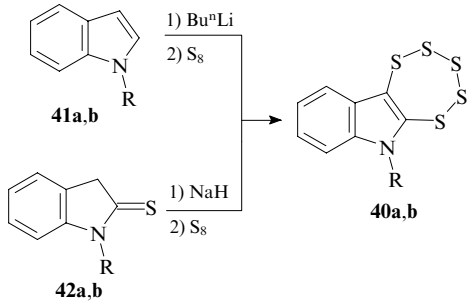
R = Ph (87%), 4-MeC_6H_4 (65%), 4-ClC_6H_4 (56%), 1-adamantyl (19%).

It should also be noted that benzopentathiepine (**1a**) was obtained as one of products in the reaction of dehydrobenzene with sulfur at low temperature.[33] Unlike the above-considered reactions, this reaction results in the addition of elemental sulfur to the carbon–carbon triple bond.



1a (12%)

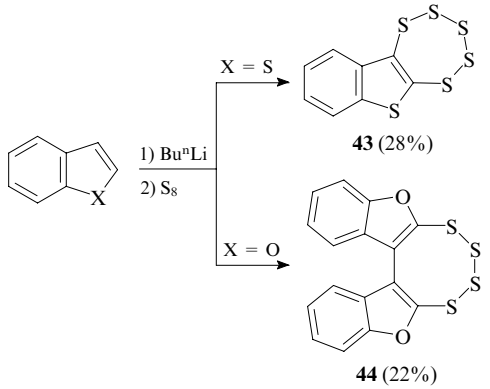
2,3-Benzannulated five-membered heterocycles containing one heteroatom readily react with electrophilic sulfur in the presence of strong bases. In these reactions, the double bond of the starting molecule, which is involved in the heteroaromatic system, remains intact, and the process can be considered as the formal replacement of hydrogen atoms. Pentathiepino[6,7-*c*]-indoles **40a**,**b** were synthesised by Bergman and co-workers [34] from indole derivatives **41a**,**b** and thiooxindole **42a**,**b**. The reaction with sulfur is preceded by the treatment of the heterocycles by butyllithium or sodium hydride.



41a,**b** **42a**,**b** **40a**,**b**

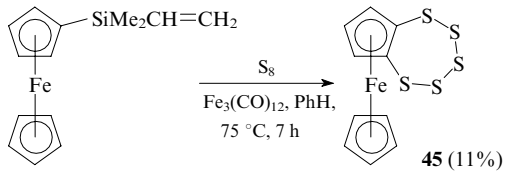
Starting compound	R	Yield of **40** (%)
41a	H	29
41b	Me	22
42a	H	42
42b	Me	13

The reaction of benzo[*b*]thiophene with butyllithium and S_8 produces benzothienopentathiepine **43**, whereas the reaction of benzo[*b*]furan performed under analogous conditions gives only bis(benzofuro)tetrathiocine **44**.[35]



43 (28%) **44** (22%)

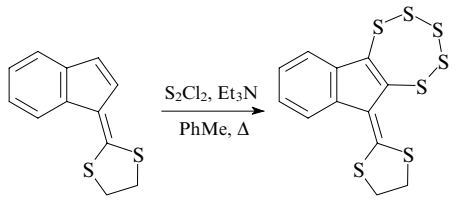
In the presence of a mixture of elemental sulfur and iron carbonyl $Fe_3(CO)_{12}$, (vinyldimethyl)silylferrocene is transformed into the corresponding pentathiepine fused with ferrocene (**45**).[36] In this reaction, not only the hydrogen atom, but also the silicon-containing group are replaced.



45 (11%)

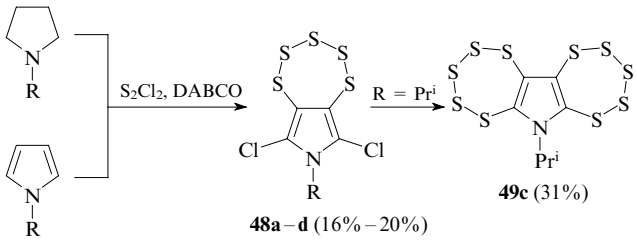
b. Reactions with sulfur monochloride

Commercially available sulfur monochloride is used as a reagent for cyclosulfurisation of various compounds to form pentathiepines. For example, refluxing of indene derivative **46** in toluene with S_2Cl_2 in the presence of triethylamine afforded pentathiepine **47**.[37] Apparently, the initial electrophilic replacement of two hydrogen atoms gives rise to a 2,3-bis(chlorodithio) derivative, which reacts with the third sulfur monochloride molecule to form the pentathiepine ring after elimination of SCl_2.



46 **47** (14%)

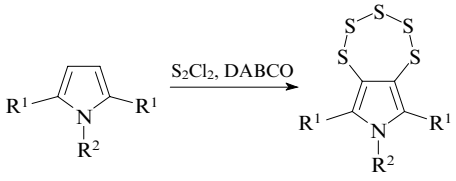
Recently, we have demonstrated [38, 39] that the reactions of five-membered electron-donating heterocycles, such as pyrrole, thiophene and their derivatives, with S_2Cl_2 in the presence of a base can be used as a one-pot method for the synthesis of annulated pentathiepines. Pentathiepines **48a**–**d** fused at positions 3 and 4 of the pyrrole ring were synthesised from *N*-substituted pyrroles and pyrrolidines. These reactions are also accompanied by the replacement of the hydrogen atoms in the β position. It should be noted that the reaction of *N*-isopropylpyrrolidine with S_2Cl_2 and DABCO produced pyrrolobis(pentathiepine) **49c**, which is the first representative of compounds containing two pentathiepine rings in one molecule.



48a–**d** (16%–20%) **49c** (31%)

R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**).

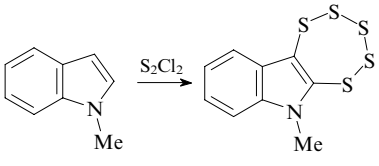
In the reactions with 1,2,5-trisubstituted pyrroles, cyclosulfurisation products **48a**,**e**–**i** are formed in good yields.



48a,**e**–**i** (74%–85%)

R^1 = Cl, R^2 = Me (**a**); R^1 = Me: R^2 = Me (**e**), Et (**f**), Pr^n (**g**), Pr^i (**h**), CH_2Ph (**i**).

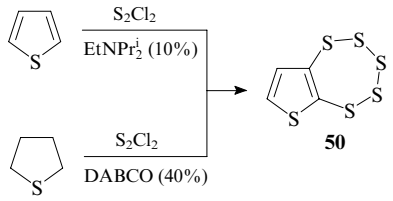
Under analogous conditions, the reaction of *N*-methylindole produced pentathiepino[6,7-*c*]indole **40b**.



40b (72%)

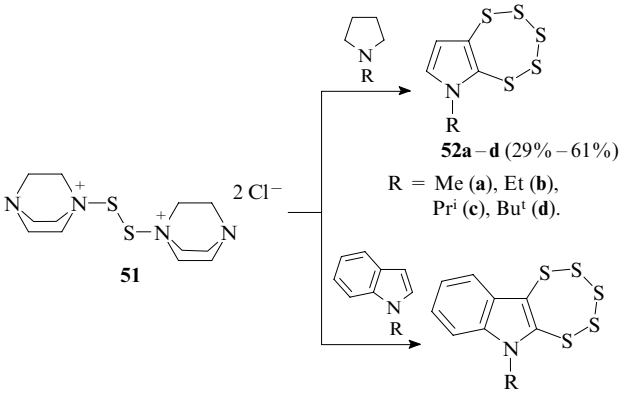
The reaction of thiophene with S_2Cl_2 in the presence of diisopropylethylamine gives pentathiepine **50** in substantially

lower yield than that obtained in the reaction of tetrahydrothiophene with S_2Cl_2 in the presence of DABCO.



50

Pentathiepines fused with the pyrrole, thiophene or indole rings can also be prepared by the reactions of the corresponding heterocycles with a prestored mixture of sulfur monochloride and DABCO.[40] The authors hypothesised that 1-(4-aza-1-azoniabicyclo[2.2.2]oct-1-yldithio)-4-aza-1-azoniabicyclo-[2.2.2]octane dichloride (**51**) is the main reacting species in these transformations. The formation of the latter was established by IR spectroscopy based on the disappearance of the S–Cl absorption band. It should be noted that in these reactions, annulation products **52a–d** at positions 2 and 3 of the pyrrole ring are generated from *N*-substituted pyrrolidines.



51

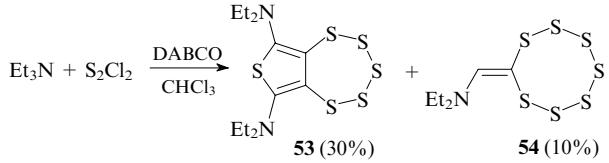
52a–d (29%–61%)

R = Me (**a**), Et (**b**), Pr^i (**c**), Bu^t (**d**).

40b,c

R = Me (**b**, 51%), Et (**c**, 62%).

High reactivity of salt **51** was confirmed by its unexpected transformations. For example, the addition of triethylamine to a solution of this salt in chloroform followed by heating of the reaction mixture afforded thienopentathiepine **53** and heptathiocane **54**.[41] X-Ray diffraction study demonstrated that the polysulfur rings of these compounds exist as chair and crown conformations, respectively.



53 (30%) **54** (10%)

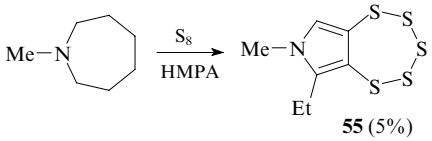
The reactions of other tertiary ethylamines with S_2Cl_2 proceed analogously, although these reactions afford products in lower yields. The thiophene ring in compound **53** is constructed from the ethyl groups of two amine molecules (the new C–C bond is formed between two non-activated methyl groups); the pentathiepine ring, as a result of the reaction of intermediate thiophene with salt **51** (by analogy with the above-considered examples). The probable reaction mechanisms were proposed in the cited studies.

In spite of low yields of the products, the advantage of this method is that these products are generally formed in one step from cheap starting reagents.

4. Other methods

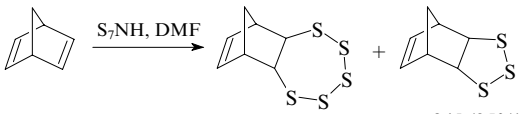
In conclusion, let us consider several original approaches to the synthesis of pentathiepines.

Cyclosulfurisation with elemental sulfur accompanied by the intramolecular rearrangement of the starting compound was documented. The reaction of *N*-methylazepane with sulfur in the presence of hexamethylphosphoramide (HMPA) produced pentathiepinopyrrole **55** in low yield.[42] Unfortunately, no suggestions about the reaction mechanism were made.



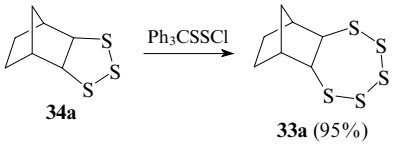
55 (5%)

In some cases, pentathiepanes and pentathiepines were synthesised with the use of non-traditional reagents. For example, pentathiepane **33d** was synthesised from norbornadiene with the use of the sulfurising reagent S_7NH, which is more reactive than elemental sulfur (see Section II.3.a). Although the reaction was performed under mild conditions (at room temperature), pentathiepane **33d** was produced in low yield (12%), and trithiole **34d** was obtained as the major product.[27]



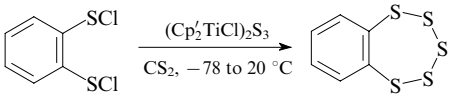
33d (12%) **34d** (25%)

Structurally similar trithiole **34a** was transformed into the corresponding pentathiepane **33a** in high yield in the reaction with triphenylmethylthiosulfenyl chloride (Ph_3CSSCl).[43]



34a **33a** (95%)

One of the most rational methods for the synthesis of pentathiepines is based on the introduction of three sulfur atoms into 1,2-bis(chlorosulfenyl)benzene under the action of bis(pentamethylcyclopentadienyl)titanium dichloride trisulfide. This reaction gives benzopentathiepine (**1a**) in good yield.[44]

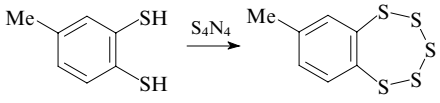


1a (73%)

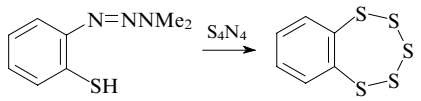
Cp′ = η-C_5Me_5.

This method was also used for the synthesis of pentathiepane **33b** from the corresponding bis(sulfenyl chloride). This reaction produced compound **33b** in 9% yield.[45]

Tetrasulfur tetranitride (S_4N_4) can also be used as the sulfurising reagent in the synthesis of benzopentathiepines. For example, refluxing of S_4N_4 in xylene with 4-methylbenzene-1,2-dithiol and (*ortho*-mercaptophenyl)triazene[46] afforded compounds **1l** and **1a**, respectively.

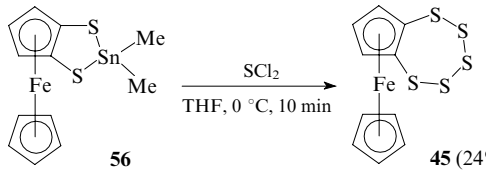


1l (58%)



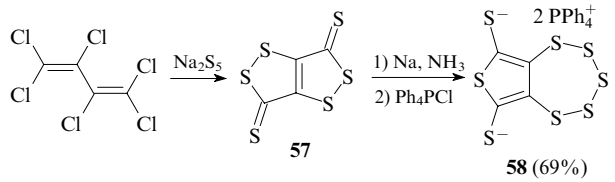
1a (29%)

Pentathiepine fused with ferrocene (**45**) was synthesised by the reaction of dithiastannole **56** with a large excess of sulfur dichloride.[47]



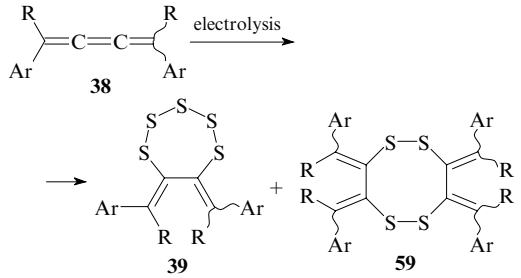
56 **45** (24%)

Perchlorobuta-1,3-diene reacts with Na_2S_5 to form bis(dithiolethione) **57**. The reaction of the latter with sodium in liquid ammonia followed by the treatment with $Ph_4P^+Cl^-$ affords thienopentathiepine salt **58**.[48]



57 **58** (69%)

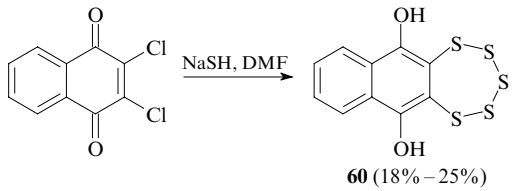
Sulfurisation of 1,1,4,4-tetrasubstituted buta-1,2,3-trienes **38** to form pentathiepanes can be performed by electrolysis on a sulfur graphite electrode in DMF in the presence of Et_4NOTs.[49,50] The reactions with tetraaryl derivatives **38** (R = Ar) afforded pentathiepanes **39** (R = Ar) as the major products (61%–86% yields). By contrast, 1,4-bis(trifluoromethyl)-1,4-diarylbuta-1,2,3-trienes gave predominantly 1,2,5,6-tetrathiocines **59**, whereas pentathiepanes **39** ($R = CF_3$) were isolated in yields from 1% to 25%.



38 **39** **59**

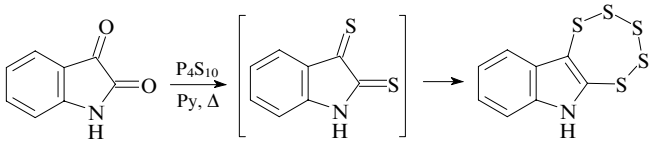
R = CF_3 or Ar; Ar = 4-XC_6H_4 (X = H, Me, Cl, MeO).

Some approaches to the synthesis of pentathiepines were discovered accidentally. For example, the reaction of 2,3-dichloro-1,4-naphthoquinone with sodium hydrosulfide in DMF unexpectedly produced naphthopentathiepine **60**.[51]



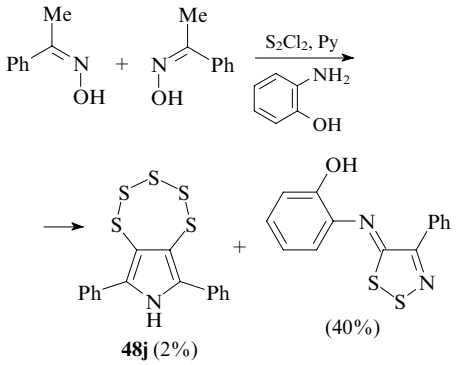
60 (18%–25%)

It appeared that the reaction of isatin with P_4S_{10} under reflux in pyridine does not stop at the formation of dithioisatin; instead, it produces pentathiepino[6,7-*c*]indole **40a**. This fact is indicative of thermodynamic stability of the final products, fused pentathiepines.[52]



40a (7%)

Pentathiepino[6,7-*c*]pyrrole **48j** was isolated as a by-product in the reaction of acetophenone oxime with sulfur monochloride in the presence of pyridine and *o*-aminophenol.[53] This reaction gives substituted dithiazole as the major product.

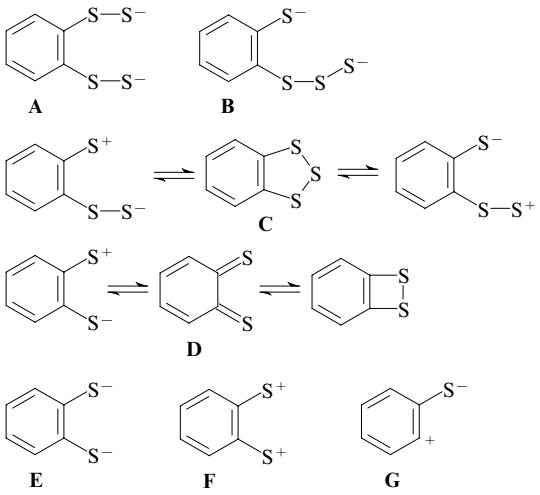


48j (2%) (40%)

To summarise, there are several approaches to the construction of the pentathiepine ring based on different starting compounds and sulfur-containing reagents.

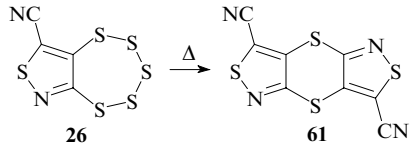
III. Chemical properties

Most reactions of pentathiepines and pentathiepanes considered in this Section involve the nucleophilic or electrophilic attack on the S atom, resulting in the pentathiepine ring opening and elimination of one to five sulfur atoms.[54] These reactions proceed through the formation of various charged and neutral intermediates **A**–**G**.[55]



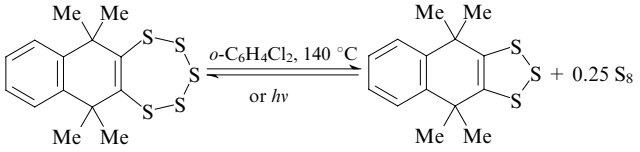
1. Thermolysis and photolysis

Thermal and photochemical transformations of pentathiepines generally lead to a loss of two, three or four sulfur atoms. These reactions produce 1,2,3-trithioles, dimeric tetrathiocines and 1,4-dithiines. For example, pyrolysis of pentathiepinoisothiazole **26** affords 1,4-dithiine **61**.[17]



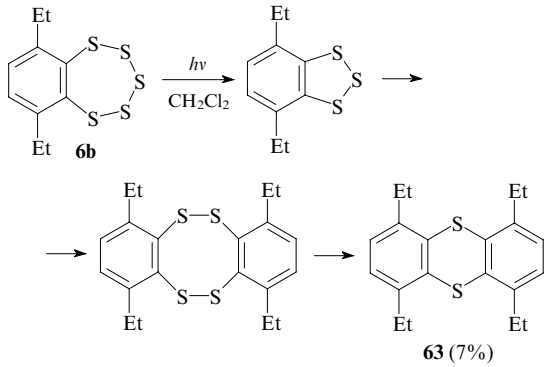
26 **61**

Heating of dihydronaphthopentathiepine **21** in 1,2-dichlorobenzene to 140 °C or its irradiation with a high-pressure mercury lamp (100 W) affords an equilibrium mixture of the starting pentathiepine, 1,2,3-trithiole **62** and elemental sulfur.[56]



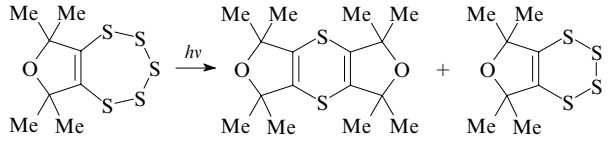
21 **62**

Irradiation of a solution of 6,9-diethylbenzopentathiepine (**6b**) in dichloromethane leads to successive desulfurisation, dimerisation and ring contraction. The corresponding trithiole and tetrathiocin were detected as intermediates, and 1,4-dithiine **63** was obtained as the final transformation product.[57]



63 (7%)

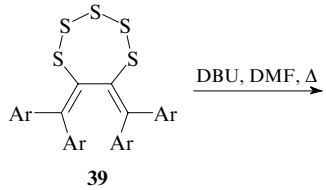
Under analogous conditions, dihydropentathiepino[6,7-*c*]-furan **18** also gave 1,4-dithiine **64**; however, compound **65** belonging to the poorly known class of 1,2,3,4-tetrathiines was isolated as the major photolysis product.[16]



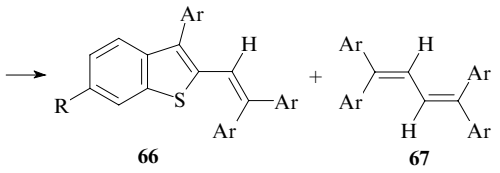
18 **64** (20%) **65** (70%)

2. Desulfurisation with bases

The reactions of pentathiepines and pentathiepanes with bases {for example, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and other tertiary or secondary amines} involve desulfurisation of the substrate accompanied by a loss of two to five sulfur atoms. For example, refluxing of pentathiepanes **39** in the presence of DBU in DMF affords the corresponding benzothiophenes **66** and buta-1,3-dienes **67**.[32] In the authors' opinion, the mechanism of formation of these products and their



39

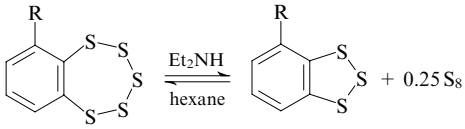


66 **67**

Ar	Yield (%)	
	66	**67**
Ph	12	52
4-MeC_6H_4	33	40
4-ClC_6H_4	2	32

ratio depend on the relative stability and reactivity of radical intermediates.

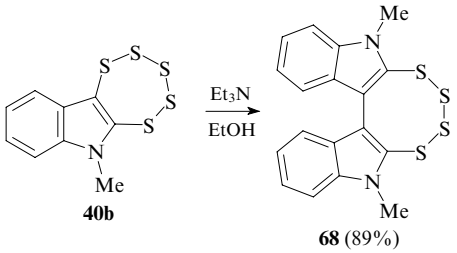
The reactions of benzopentathiepines **1o**,**p**,**t** substituted at position 6 with diethylamine in hexane yield the corresponding trithioles **5o**,**p**,**t**.[15] In the reaction with trifluoromethyl derivative **1p**, an equilibrium is established (**1p** : **5p** = 46 : 54).



1o,**p**,**t** **5o**,**p**,**t**

R = Br (**o**), CF_3 (**p**), CH_2CO_2Me (**t**).

Heating of pentathiepino[6,7-*c*]indole **40b** with triethylamine in ethanol affords bis(indolo)-fused 1,2,3,4-tetrathiocine **68** in high yield.[34] The reaction mechanism involves elimination of three sulfur atoms to form dithioindole, which undergoes dimerisation to give product **68**.

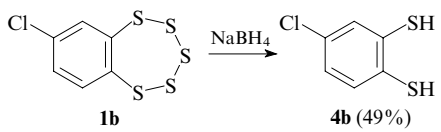


40b **68** (89%)

Evidently, the role of the base in these transformations is to cleave the polysulfide chain.

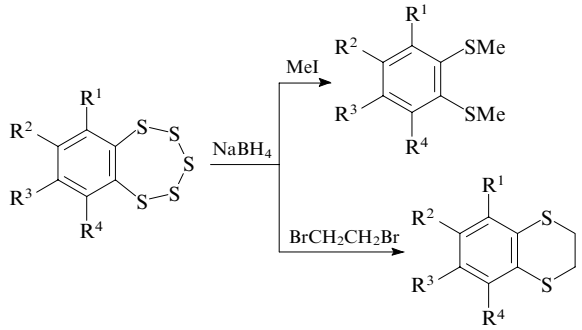
3. Reduction

Benzopentathiepines are reduced most often with sodium borohydride.[15] These reactions generally produce arene-1,2-dithiols. For example, 7-chlorobenzopentathiepine (**1b**) was reduced with $NaBH_4$ to dithiol **4b**.[15]



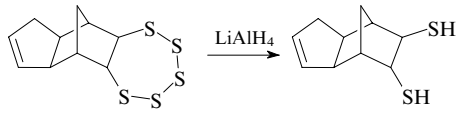
1b **4b** (49%)

In the presence of an electrophilic reagent (for example, alkyl halide) in the reaction mixture, intermediate dithiol is readily alkylated to form stable 1,2-di(alkylthio) derivatives. *S*,*S*-Dialkyl-substituted arene-1,2-dithiols were synthesised from various benzopentathiepines according to this method.[11, 13, 15]



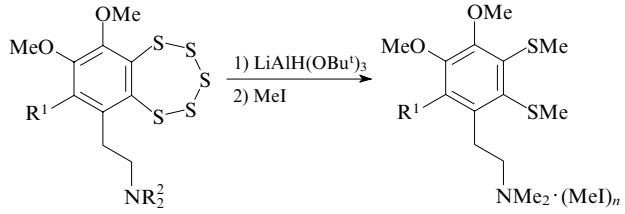
$R^1 = R^3 = R^4 = H$: $R^2 = Cl, NMe_2$;
$R^1 = R^4 = Me$: $R^2–R^3 = –SSS–, –SCH_2CH_2S–$;
$R^1 = R^4 = OMe$, $R^2–R^3 = –SSS–$.

1,2-Dithiol **69** was prepared from pentathiepane **33b** with the use of lithium aluminium hydride. Compound **69** is rather stable; it was isolated in almost quantitative yield and characterised by different physicochemical methods.[27]



33b **69** (96.5%)

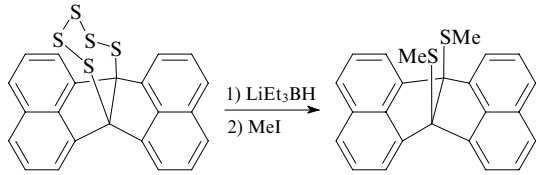
Varacin (**2a**) and its derivative **3a** were reduced with lithium tris(*tert*-butoxy)aluminium hydride.[58, 59] Subsequent alkylation of the intermediate with iodomethane afforded amine **70a** and quaternary ammonium salt **71a**, respectively.



2a: $R^1 = R^2 = H$;
3a: $R^1 = SMe$, $R^2 = Me$

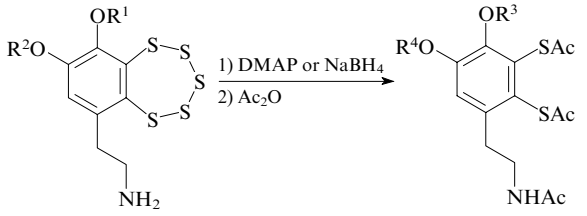
70a: $R^1 = H$, $n = 0$;
71a: $R^1 = SMe$, $n = 1$

Polycyclic pentathiepane **37** was reduced with lithium triethyl borohydride. The treatment of the reaction mixture with iodomethane gave the bis(methylthio) derivative of acenaphtho[1,2-*a*]-acenaphthene **72**.[31]



37 **72**

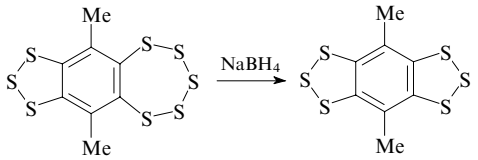
The reactions can be performed with acylating reagents instead of alkylating reagents. For example, the reaction of lissoclinotoxin A (**2b**) with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in DMF at room temperature produces compound **73b**.[60] Apparently, three sulfur atoms are eliminated through the nucleophilic attack of DMAP. In the analogous reaction (with $NaBH_4$ and acetic anhydride), isolissoclinotoxin A (**2c**) gives isomer **73c**.[22]



2b: $R^1 = Me$, $R^2 = H$;
2c: $R^1 = H$, $R^2 = Me$

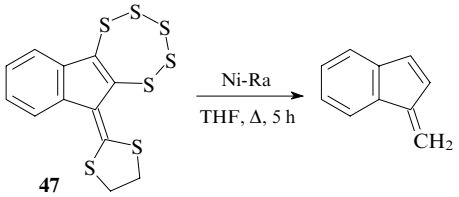
73b: $R^3 = Me$, $R^4 = Ac$;
73c: $R^3 = Ac$, $R^4 = Me$

It should be noted that the pentathiepine ring can be reduced in such a way that the trithiole ring remains intact. For example, mild reduction of trithiolobenzopentathiepine **11e** with sodium borohydride afforded benzobis(trithiole) **15** in good yield.[13]



11e **15** (66%)

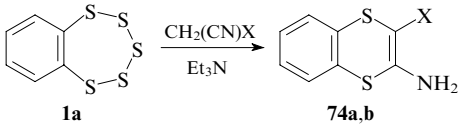
Pentathiepine **47** is reduced under reflux with Raney nickel in THF with a loss of all five sulfur atoms and cleavage of the dithiole ring to form benzofulvene.[37]



47

4. Reactions with compounds containing the activated methylene group

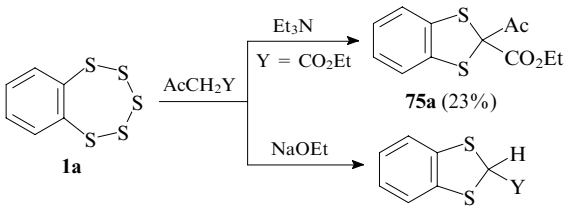
In the presence of bases (triethylamine or sodium ethoxide), compounds containing the CH-acidic methylene group (malononitrile, ethyl cyanoacetate, ethyl acetoacetate, ethyl 2-chloropropionate and acetylacetone) react with benzopentathiepine (**1a**) to form 1,4-dithiines, 1,3-dithioles and 1,2,4-trithiines.[61] Under these conditions, malononitrile and ethyl cyanoacetate give dithiines **74** in high yields.



1a **74a,b**

X = CN (**a**, 87%), CO_2Et (**b**, 76%).

The reaction of benzopentathiepine (**1a**) with ethyl acetoacetate in the presence of triethylamine produces benzo-1,3-dithiole **75a**; the reaction with ethyl acetoacetate and acetyl-

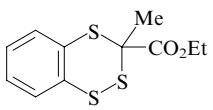


1a **75a** (23%)

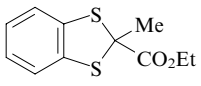
75b: Y = CO_2Et (57%);
75c: Y = Ac (42%)

acetone in the presence of sodium ethoxide gives benzodithioles **75b**,**c**.

Dithioles **75a** (40% yield) and **75b** (42%) are formed also from benzopentathiepine (**1a**) and ethyl 2-chloroacetoacetate. However, the reaction of compound **1a** with ethyl 2-chloropropionate and sodium ethoxide gives trithiine **76** rather than dithiole **75d** as the major product. Presumably, the latter reaction proceeds through the above-considered intermediates **C**, **D** or **F** (see the beginning of Section III).



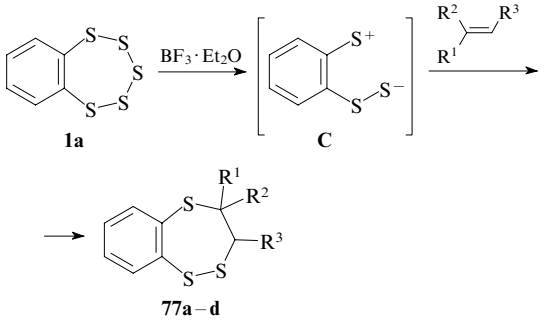
76 (74%)



75d (7%)

5. Reactions with unsaturated compounds

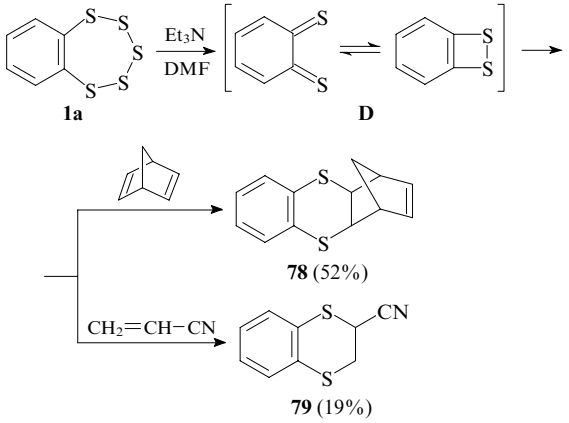
The reactions of benzopentathiepines with unsaturated compounds (alkenes, alkynes and arenes) give rise to new S–C bonds. Benzopentathiepine (**1a**) reacts with alkenes in the presence of a Lewis acid or triethylamine. The reaction catalysed by $BF_3 \cdot Et_2O$ produces unsymmetrical benzo-1,2,5-trithiepines **77a**–**d**. In this case, pentathiepine is involved in the reaction as a 1,5-dipole (**C**).[62] Other Lewis acids are less efficient catalysts for the pentathiepine ring opening than $BF_3 \cdot Et_2O$.



1a **C** **77a**–**d**

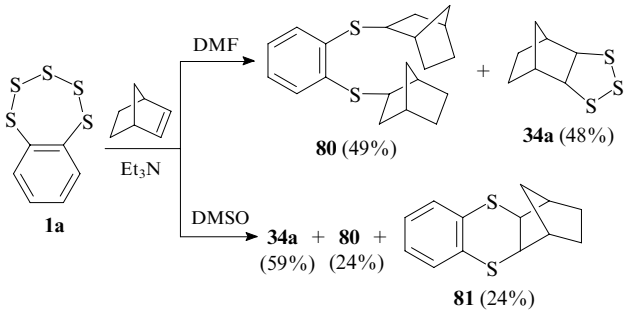
Compound **77**	R^1	R^2	R^3	Yield (%)
a	H	$(CH_2)_4$		81
b	H	$(CH_2)_3$		68
c	Me	H	Me	58
d	Et	H	Et	39

In the presence of triethylamine in DMF, the reaction of compound **1a** with norbornadiene and acrylonitrile is accompanied by a loss of three sulfur atoms; 1,4-dithianes **78** and **79** are apparently formed through intermediate **D**.[55]



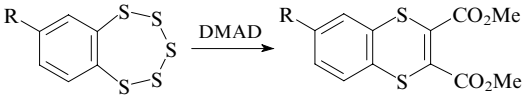
1a **D** **78** (52%) **79** (19%)

The direction of the reaction of benzopentathiepine (**1a**) with norbornene in the presence of triethylamine depends on the nature of the solvent. The reaction in DMF produces an equimolar mixture of 1,2,3-trithiolane **34a** and adduct **80** generated as a result of addition of two norbornene molecules at the sulfur atoms. The analogous reaction in DMSO gives not only compounds **34a** and **80**, but also dithiane **81**.



1a **80** (49%) **34a** (48%) **34a** + **80** + (59%) (24%) **81** (24%)

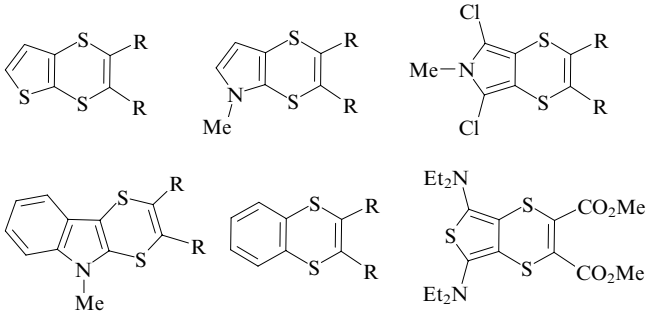
Benzopentathiepines **1a**,**b**,**q** slowly react with dimethyl acetylenedicarboxylate (DMAD) to form benzo-1,4-dithiines **82a**,**b**,**q**, the reaction being substantially accelerated in the presence of triphenylphosphine or triethylamine in DMF.[15,55]



1a,**b**,**q** **82a**,**b**,**q**

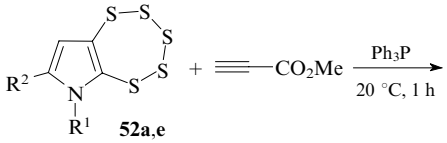
Product **82**	R	Reaction conditions	Yield (%)
a	H	Et_3N, DMF	84
b	Cl	xylene	15
q	NMe_2	Ph_3P, CH_2Cl_2	51

The reaction of electron-withdrawing alkynes with pentathiepines fused with aromatic and heterocyclic rings in the presence of triphenylphosphine is characteristic of this class of compounds; the corresponding 1,4-dithiines are formed in high yields (64%–93%).[41,63] Examples of compounds prepared according to this procedure are given below.

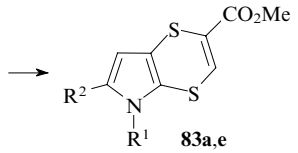


R = CO_2Me, C(O)Ph.

In the presence of triphenylphosphine, pentathiepino-[6,7-*b*]pyrroles **52a**,**e** regioselectively add to an unsymmetircal alkyne molecule.[63] For example, in compliance with the electron density distribution in the intermediates, which are generated according to the proposed reaction mechanism, the addition products of methyl propiolate, *viz*., fused 1,4-dithiines **83a**,**e**, were obtained.



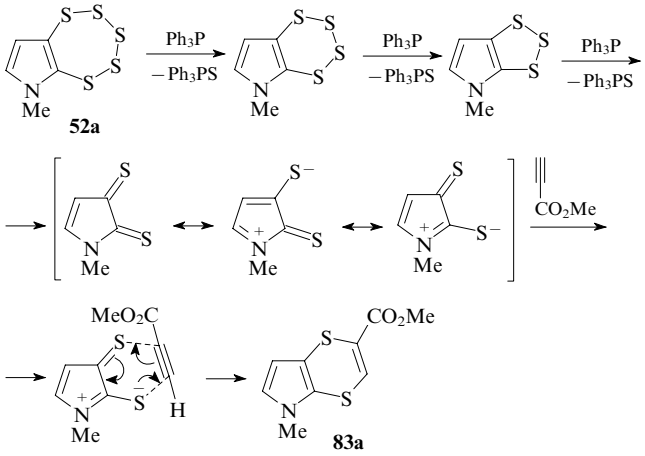
52a,**e**



83a,**e**

R^1 = Me, R^2 = H (**a**); R^1 = Et, R^2 = Cl (**e**).

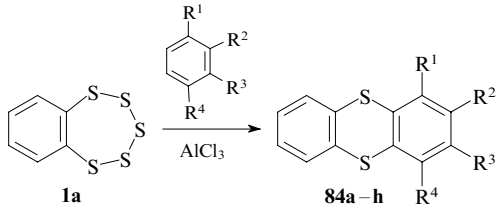
Apparently, triphenylphosphine, acting as a nucleophile, attacks molecule **52a**, which is accompanied by the pentathiepine ring opening and successive elimination of three sulfur atoms to give intermediate of type **D**,[55] and the latter adds to alkyne (see also Section III.6, the reaction with the Grignard reagent).



52a

83a

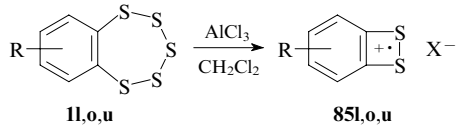
Benzopentathiepine (**1a**) reacts with benzene and some its derivatives in the presence of a Lewis acid (for example, $AlCl_3$) as the catalyst. The corresponding 1,4-dithiines **84a**–**h** are generally formed in good yields.[64]



1a **84a**–**h**

Compound **84**	R^1	R^2	R^3	R^4	Yield (%)
a	H	H	H	H	44
b	Me	H	H	Me	75
c	Pr^i	H	H	Pr^i	62
d	Me	Me	Me	Me	83
e	1,2-C_6H_4		H	H	93
f	Me	1,2-SC_6H_4S		Me	20
g	H	H	1,2-C_6H_4S		43
h	H	H	1,2-C_6H_4S		43

Under the action of $AlCl_3$ in dichloromethane, pentathiepines **1l**,**o**,**u** are transformed into radical cations **85l**,**o**,**u**, which are apparently intermediates in Friedel–Crafts reactions.[65] The formation of radical cations **85** was detected by EPR spectroscopy.

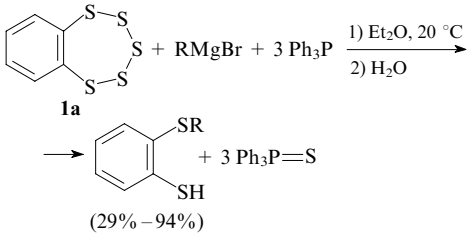


1l,**o**,**u** **85l**,**o**,**u**

R = 7-Me (**l**), 6-Br (**o**), 7-CF_3 (**u**); X = Cl or $AlCl_4$.

6. Reactions with Grignard reagents

R Sato *et al.*[66] developed convenient procedures for the synthesis of 2-alkyl(aryl)sulfenylthiophenols. These authors demonstrated that benzopentathiepine (**1a**) reacts with alkyl- and arylmagnesium bromides under mild conditions in the presence of triphenylphosphine.



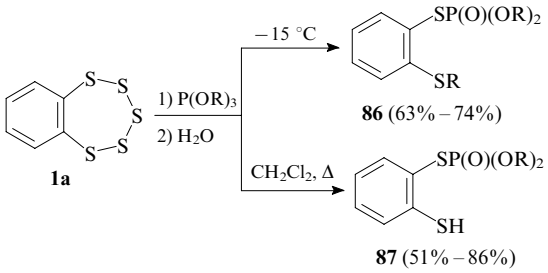
1a

R = Alk, Ar.

In the absence of triphehylphosphine, the reactions give products in low yields. The presumable mechanism of these reactions involves elimination of three sulfur atoms from benzopentathiepine (**1a**) under the action of triphehylphosphine to form intermediate of type **D**, which adds a Grignard reagent. Hydrolysis of the reaction mixture leads to organylsulfenylthiophenols.

7. Reactions with phosphorus-containing compounds

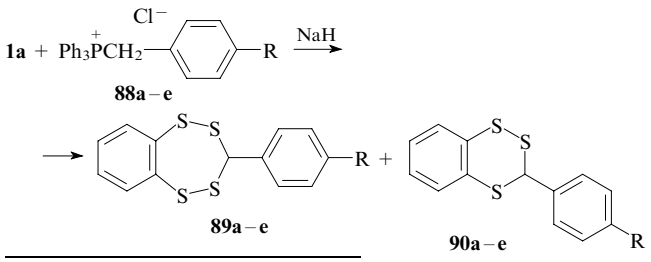
The reactions of benzopentathiepine (**1a**) with neutral and cationic organophosphorus compounds were documented. The reactions with trialkyl phosphites regioselectively produce thiophosphonates **86** or **87** depending on the reaction conditions.[67] The former products are generated at −15 °C; the latter products, under reflux of the reagents in dichloromethane. Apparently, the reaction is accompanied by elimination of three sulfur atoms under the action of $P(OR)_3$, and the resulting intermediate **D** adds the phosphite molecule.



1a **86** (63%–74%) **87** (51%–86%)

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

The nucleophilic attack on benzylphosphonium salts **88** in the presence of sodium hydride in pentathiepine **1a** results in a mild ring opening.[68] These reactions produce mixtures of tetrathiepines **89** and trithiines **90** in moderate yields.

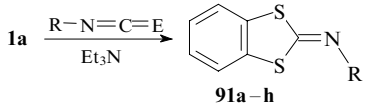


88a–**e** **89a**–**e** **90a**–**e**

Compound	R	Yields (%)	
		89	**90**
a	H	15	52
b	NO_2	0	55
c	Me	19	51
d	OMe	45	25
e	Cl	7	53

8. Reactions with isothiocyanates

2-Iminobenzo-1,3-dithioles **91a–h** were synthesised in good yields from benzopentathiepine (**1a**) and isothiocyanates in the presence of triethylamine.[69] Aryl isothiocyanates react more readily than alkyl derivatives, and their reactions are accelerated in the presence of electron-donating groups in the molecule. However, unsubstituted phenyl isothiocyanate does not react with pentathiepine **1a**, and compound **91h** was synthesised with the use of phenyl isoselenocyanate.

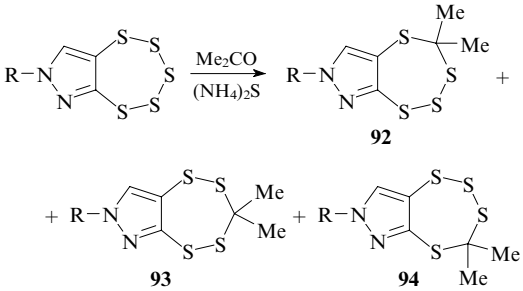


91a–h

E = S: R = Me (**a**, 81%), Et (**b**, 59%), Pr^n (**c**, 47%), 4-MeC$_6$H$_4$ (**d**, 77%), 4-ClC$_6$H$_4$ (**e**, 84%), 4-MeOC$_6$H$_4$ (**f**, 74%), 2-MeOC$_6$H$_4$ (**g**, 86%);
E = Se, R = Ph (**h**, 78%).

9. Reactions with acetone

Condensation of pentathiepino[6,7-*c*]pyrazoles with acetone in the presence of ammonium sulfide at room temperature gives a mixture of tetrathiepines **92–94** in low yields.[70]



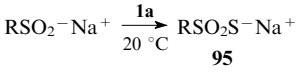
92 **93** **94**

R	Yield (%)		
	92	**93**	**94**
Me	10	15	0
Ph	22	21	14

The structures, the energies of transformation and conformational dynamics of isomeric tetrathiepines were studied. However, the mechanism of formation of these compounds remains unclear. Presumably, the pentathiepine ring is cleaved as a result of the nucleophilic attack of the sulfide ion. This reaction is accompanied by extrusion of S_2 to form bis-nucleophilic intermediates analogous to intermediates **A** and **B**, which are fused with acetone.

10. Unusual transformations of pentathiepines

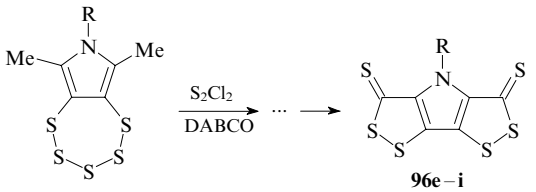
Pentathiepines can serve as sources of sulfur atoms. For example, in the reactions with benzopentathiepine (**1a**), sodium alkyl- and arylsulfinates are transformed into thiosulfonates **95** in high yields.[71]



95

R = Me (78%), Ph (99%), PhCH$_2$ (81%), PhCH$_2$CH$_2$ (86%), Cl(CH$_2$)$_4$ (78%), 4-MeC$_6$H$_4$ (100%), 4-ClC$_6$H$_4$ (82%), 4-MeOC$_6$H$_4$ (96%), 4-BrC$_6$H$_4$ (85%), EtO$_2$CCH$_2$CH$_2$ (69%).

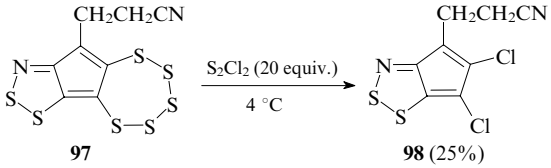
The treatment of *N*-substituted pentathiepino[6,7-*c*]pyrroles **48e–i** with a prestored mixture of sulfur monochloride and DABCO at room temperature leads to an unusual cascade transformation giving rise to bis(dithiolo)pyrroles **96e–i** in high yields.[39] The authors described the presumable reaction mechanism involving oxidation of an enamine tautomer with a disulfide reagent as the key step.



48e–i **96e–i**

R = Me (**e**, 85%), Et (**f**, 80%), Pr^n (**g**, 74%), Pr^i (**h**, 79%), CH$_2$Ph (**i**, 84%).

The treatment of pentathiepine **97** with a large excess of S_2Cl_2 unexpectedly leads to elimination of all sulfur atoms to form vicinal dichloride **98**.[24] At 4 °C, the reaction is completed in a few days.



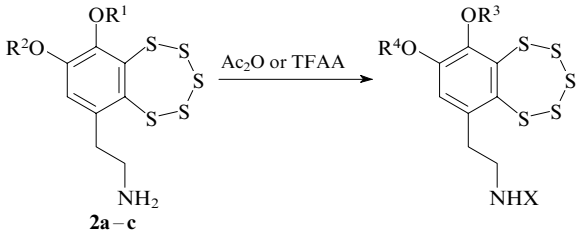
97 **98** (25%)

Analogous transformations of other pentathiepines are unknown.

11. Reactions of substituents in aromatic rings of benzopentathiepines

a. Reactions of amino and hydroxy groups

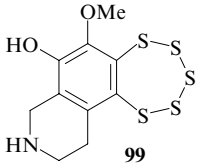
Reactions of the phenol hydroxy group and an aminoalkyl-aromatic fragment of benzopentathiepine derivatives are of interest primary as procedures for modifying natural pentathiepines and their analogues. It should be noted that the pentathiepine ring is very sensitive to the nucleophilic attack, for example, by the nitrogen atom of the unsubstituted amino group of a peripheral substituent.[8] For this reason, the protection of the amino group by acylation leads to substantial stabilisation of pentathiepines. *N*-Acetylation and trifluoroacetylation of amines are generally performed with acetic [60, 72] or trifluoroacetic (TFAA) anhydrides,[22, 73] Ac_2O reacting also with free phenol groups.



2a–c

R^1 = Me: R^2 = Me (**2a**), H (**2b**); R^1 = H, R^2 = Me (**2c**); R^3 = Me, R^4 = X = Ac; R^3 = X = Ac, R^4 = Me; R^3 = R^4 = Me, X = COCF$_3$; R^3 = Me, R^4 = H, X = COCF$_3$; R^3 = H, R^4 = Me, X = COCF$_3$.

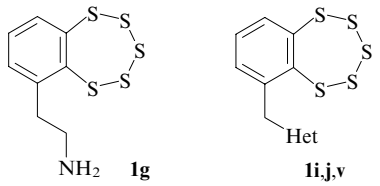
Lissoclinotoxin B (**99**) is easily acylated with acetic anhydride in pyridine at room temperature. The reaction proceeds both at the nitrogen atom of the amino group and the oxygen atom of the phenol hydroxy group.[22]



99

It should be noted that the pentathiepine ring remains intact in the transformation of the amino group of the side chain in varacin (**2a**) into the urea fragment in the course of the reaction with (*S*)-(+)-1-(1-naphthyl)ethyl isocyanate.[74]

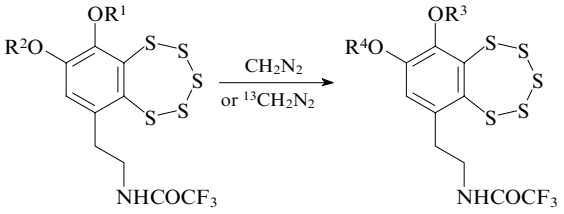
Since benzopentathiepine **1g** containing the free aminoethyl group is unstable, it is generally used as hydrochloride. By contrast, compounds **1i**,**j**,**v** containing less nucleophilic heterocyclic fragments (pyridine or pyrimidine) and thiophene are rather stable.[8]



1g **1i**,**j**,**v**

Het = 2-Py (**i**), 2-Pyrm (**j**), 2-thienyl (**v**).

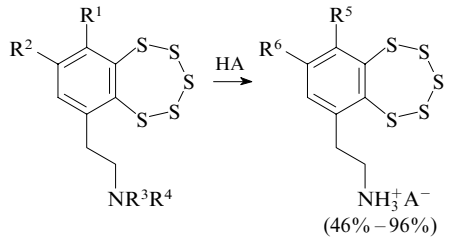
Methylation of the phenol group in compounds **2d**,**e** with diazomethane and ^{13}C-labelled diazomethane made it possible to establish the structure of lissoclinotoxin A.[73] In this reaction, the pentathiepine ring also remains intact.



2d,**e**

R^1 = H, R^2 = Me (**d**); R^1 = Me, R^2 = H (**e**);
R^3 = R^4 = Me; R^3 = Me, R^4 = $^{13}CH_3$; R^3 = $^{13}CH_3$, R^4 = Me.

Derivatives of varacin and lissoclinotoxin A containing primary or secondary amino groups can be transformed into stable hydrochlorides and trifluoroacetates.[8, 10, 22, 23]

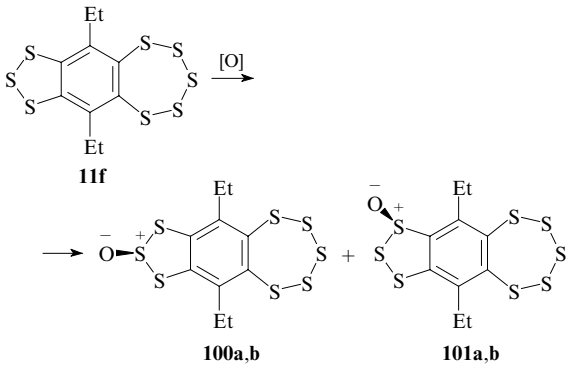


(46%–96%)

A = CF_3CO_2: R^1 = R^2 = R^5 = R^6 = OMe, R^3 = H,
R^4 = $CO_2(CH_2)_2SiMe_3$, Boc; R^1 = OCH_2OMe, R^2 = R^6 = OMe,
R^3 = H, R^4 = $CO_2(CH_2)_2SiMe_3$, R^5 = OH;
A = Cl: R^1 = R^2 = R^3 = R^5 = R^6 = H, R^4 = Boc;
R^1 = R^2 = R^5 = R^6 = OMe, R^3 = CHO, R^4 = Boc.

b. Oxidation and reduction of the trithiole ring

Tricyclic compounds **11** containing the trithiole ring along with the pentathiepine ring were oxidised with various reagents. It appeared that the reactions with *m*-chloroperoxybenzoic acid (MCPBA)[75] or the $Ti(OPr^i)_4$ – DET – Bu^tOOH [DET is (*R*,*R*)-diethyl tartrate] system[76] occur only at the trithiole ring.

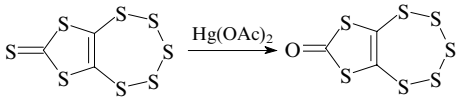


11f **100a**,**b** **101a**,**b**

Oxidant	Yield (%)			
	100a	**100b**	**101a**	**101b**
MCPBA	16	13	26	32
Bu^tOOH	29		18	23

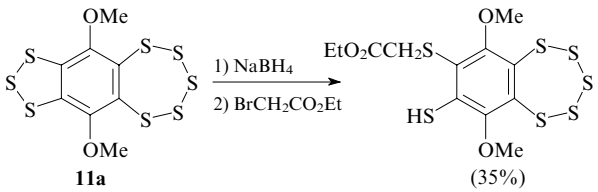
Sulfoxides **100a**,**b** and **101a**,**b** were isolated from the reaction mixture. Compounds **100a**,**b** were demonstrated to exist as achiral centrosymmetric conformers, whereas compounds **101a**,**b** are unsymmetrical diastereomers containing the sulfoxide group in different conformations with respect to the pentathiepine ring (the stereochemistry is considered in more detail in Section V).

Upon oxidation with mercury acetate, the pentathiepine ring also remains intact. For example, the reaction between this reagent and 1,3-dithiole-2-thione fused with pentathiepine **102** produces the corresponding keto derivative.[77]



102 (33%)

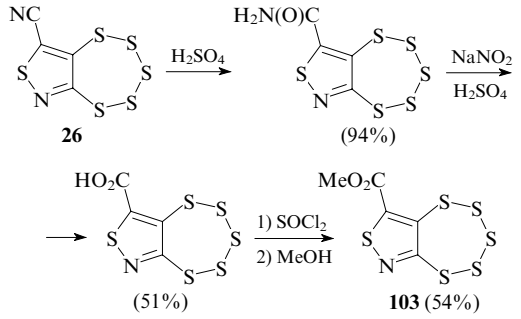
It is known that sodium borohydride $NaBH_4$ can reduce the pentathiepine ring.[15] However, the treatment of trithiolobenzopentathiepine **11a** with two equivalents of $NaBH_4$ followed by alkylation with ethyl β-bromoacetate afforded tetrasubstituted benzopentathiepine.[11] This is evidence that the trithiole ring is more sensitive to reducing reagents than the pentathiepine ring.



11a (35%)

Reactions of carboxylic acid derivatives

High stability of the pentathiepine ring to acids and nitrosating reagents was exemplified by cyanoisothiazole derivative **26**.[15] For example, the cyano group was hydrolysed in concentrated sulfuric acid to give the amide group in high yield. Then the amide was transformed under the action of sodium nitrite and concentrated sulfuric acid into the acid; its treatment with thionyl chloride and methanol afforded methyl ester **103**. In all these transformations, the pentathiepine ring remains intact.



IV. Spectroscopic studies

1. UV and IR spectroscopy

The character and positions of absorption bands in UV spectra depend on the structure of pentathiepine. The spectrum of unsubstituted pentathiepine (**24**) shows weak and diffuse signals at 206 [the extinction coefficient (ε) is 9730], 253 (ε = 3440) and 315 nm (ε = 1510).[1] Most pentathiepines are characterised by only one intense band at ~210 nm (ε = 25 000 – 32 000).[1, 15, 60, 73] The spectra of benzopentathiepines **11e**,**f** annulated with the trithiole ring show absorption bands at 292 – 294 nm (ε = 15 100 – 15 500).[78] For pentathiepines fused with pyrrole, pyrazole or thiophene, the absorption maxima are observed at 230 – 240 nm.[15, 42] The UV spectra of pentathiepanes fused with carbocycles (for example, compounds **12**, **33a**,**d** and **35**) show two characteristic bands at 231 – 233 (ε = 3750 – 5500) and 278 – 281 nm (ε = 3090 – 3480).[1, 2, 29]

The IR spectra contain absorption bands of the S – S bond in pentathiepines at 460 – 485 cm^{-1} (Ref. 29).

2. Raman spectroscopy

All pentathiepines fused with aromatic or heterocyclic rings are characterised by strong absorption at 485 cm^{-1} in Raman spectra.[15] Most often, Raman spectra of pentathiepines show two absorption bands, the most intense band being observed at 490 ± 5 cm^{-1}. The Raman spectra of benzopentathiepines have two additional characteristic absorption bands at 425 ± 5 cm^{-1} (of weak to medium intensity) and 180 ± 5 cm^{-1} (strong), which can be used for the identification of these compounds.

3. NMR spectroscopy

The ring protons in the ^{1}H NMR spectrum of unsubstituted pentathiepine (**24**) have a chemical shift (δ) of 7.42 ppm. The spectrum of benzopentathiepine (**1a**) is characterised by an AA′BB′ system centred at δ = 7.52.[1] The signals for the carbon atoms of the pentathiepine ring are observed in the ^{13}C NMR spectrum at low field (δ = 135 – 145).[18, 22, 32, 56, 59, 77]

The corresponding NMR spectra of pentathiepanes **33a**,**c**,**d** show signals for the ring hydrogen atoms at δ 3.93 – 4.06 and signals for the carbon atoms of the pentathiepane ring at δ 69.8 – 72.7.[27]

4. Mass spectrometry

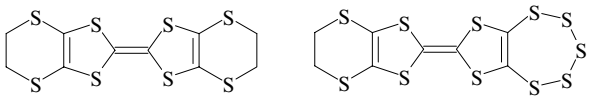
Mass spectrometry is one of the main methods for establishing the structures of pentathiepines and pentathiepanes. Generally, samples are transformed into the ionised state under electron impact. Almost in all cases, the intensity of the molecular ion peak is low (from 0.6% to 25%), and the $[M-S_2]^+$ ion peak corresponding to a loss of two sulfur atoms is the most characteristic peak (the intensity is 40% – 100%) upon fragmentation.[34, 35, 42, 46, 49, 56, 60, 77 – 79] Pentathiepines can also be identified by FAB (Fast Atom Bombardment) mass spectrometry,[72, 73] however this method has not gain wide acceptance.

5. X-Ray diffraction

The molecular structures of more than 30 compounds containing the pentathiepine or pentathiepane rings were established by X-ray diffraction. In most compounds, polysulfur-containing rings adopt a chair conformation. The S – S bond length varies from 2.039 (in benzopentathiepine **1a**)[80] to 2.063 Å (in dithiolopentathiepine **102**),[81] which is similar to the bond length in the S_8 molecule (2.051 Å). The S – S – S and S – S – S – S angles are also comparable with those in S_6 and S_8. The S – C bond lengths in pentathiepines and pentathiepanes (1.744 – 1.795 Å) are comparable with the S – C(sp^2) single bond length (1.78 Å).[15, 81, 82]

6. Electrochemical methods

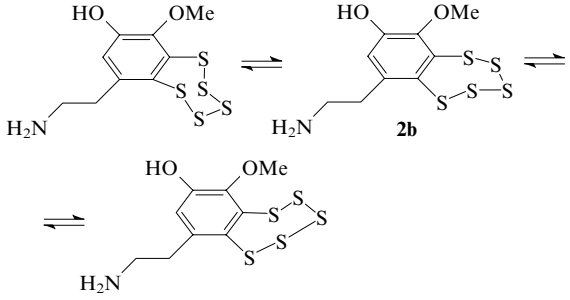
The electrochemical properties of pentathiepine **29** were studied by cyclic voltammetry. This compound is characterised by two pairs of reversible redox potentials with the following values: +0.69 and +1.06 V. These potentials are higher than those for the structurally similar BEDT-TTF compound (+0.53 and +0.89 V).[20] This indicates that the electron-donor properties of pentathiepine **29** are weaker than those of BEDT-TTF. Apparently, this fact can be attributed to the induction effect due to the larger number of sulfur atoms in the pentathiepine ring.



A comparison of the electrochemical behaviour of pentathiepinoindole **40b** and 1-methylindole demonstrated that the introduction of a polysulfur-containing ring into an inactive molecule gives rise to electrochemical activity.[83]

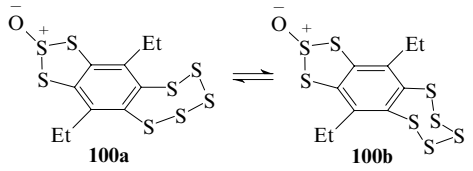
V. Stereochemical aspects: conformation and chirality

The ^{1}H NMR spectra of varacin (**2a**) and lissoclinotoxin A (**2b**) show complex signals for the protons of the benzyl group.[73, 74] A complication of the signals is a consequence of a high energy barrier (30 kcal mol^{-1}) for inversion of the pentathiepine ring, resulting in asymmetry of the molecule and diastereotopicity of the benzyl protons. An increase in temperature from 25 to 100 °C leads to narrowing of the signals and the signals for all protons are clearly observed. The high energy barrier is apparently attributed to unfavourable overlap of the isolated orbitals of the sp^3-hybridised sulfur atom during ring inversion through the half-chair transition state.[73]

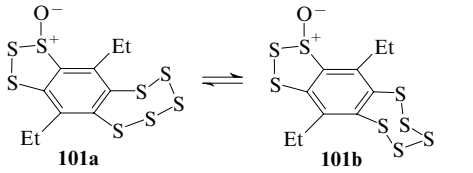


The structures of four sulfoxides (**100a**,**b** and **101a**,**b**), which were synthesised by oxidation of trithiolobenzopentathiepine **11f** with *m*-chloroperoxybenzoic acid, were estab-

lished by X-ray diffraction.[75] For pairs of 2- and 1-oxides, the activation parameters of the pentathiepine ring inversion in chloroform at room temperature were determined. It appeared that the free energy change ($^{298}\Delta G^{\neq}$) after complete inversion is from 105.0 to 113.4 kJ mol^{-1} in each case.[76]

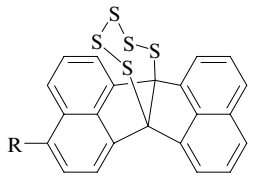


100a **100b**

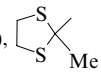


101a **101b**

Analogous investigations were performed for pairs of isomers of monosubstituted pentathiepanoacenaphtho[1,2-*a*]acenaphthylenes **37a–c**; for the complete inversion, $^{298}\Delta G^{\neq}$ was 103.8–108.5 kJ mol^{-1}.[31]



37a–c

R = Et (**a**), Ph (**b**),  (**c**).

VI. Quantum-chemical calculations of pentathiepine molecules

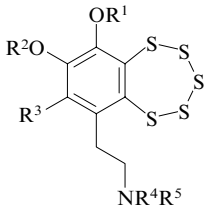
The conformations of pentathiepine (**24**), benzopentathiepine (**1a**) and thieno[3,4-*f*]pentathiepine (**1v**) were studied by the semiempirical AM1 method.[84] It was found that the rigid chair-like conformation of the heterocycle is the most stable one. The results of calculations by the CNDO method correlate well with the observed positions of absorption bands in UV spectra.

Ab initio molecular orbital calculations (SCF and MP-2) of the conformational behaviour of benzopentathiepine (**1a**) are in good agreement with the experimental data. According to the results of calculations, the chair conformation is more stable than the boat and twist conformations.[70] Calculations of the highest occupied molecular orbital and the lowest unoccupied molecular orbital for compound **1a** by the PM3 method demonstrated that the nucleophilic attack of trialkyl phosphites occurs predominantly on the sulfur atom at position 2 to give products **86** and **87**, as was described above (see Section III.7).[67]

The structures of pentathiepines and their reactions were studied in detail by Greer[85] by density functional theory (DFT). The calculations demonstrated that decomposition of unsubstituted pentathiepine (**24**) upon the nucleophilic attack on the hydrosulfide anion unexpectedly starts with the attack on the S(1) atom rather than with the more expected attack on the S(2) atom. This gives rise to the delocalised enethiolate anion, which initiates the subsequent liberation of the S_3 species.† The S_3 molecule was detected by the reactions with norbornene and 2,3-dimethylbuta-1,3-diene; these adducts are analogous to the reaction products with S_2.[86]

VII. Biological activity and practical applications of pentathiepines

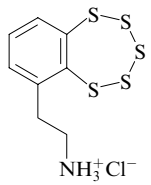
Varacin (**2a**) isolated from the marine organisms *Lissoclinum vareau* in 1991 was the first known natural pentathiepine.[58] More recently, several structurally analogous compounds were isolated: lissoclinotoxin A (**2b**) from the ascidians *Lissoclinum sp.*,[73] lissoclinotoxin B (**99**) from the tunicate *Lissoclinum perforatum* found near the Palau Islands,[60] *N,N*-dimethyl-5-(methylthio)varacin (**3a**) from the ascidians *Lissoclinum japonicum*, 5-(methylthio)varacin (**3b**) in a mixture with the corresponding trithiole (in a 2 : 3 ratio) and demethylated varacin (**2f**) from various species of the marine organisms *Lissoclinum* and *Eudistoma* found near the Pohnpei Island, respectively.[59]



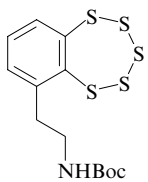
$R^1 = R^2 = Me$, $R^3 = R^4 = R^5 = H$ (**2a**);
$R^1 = R^2 = Me$, $R^3 = SMe$, $R^4 = R^5 = H$ (**3b**);
$R^2 = R^3 = R^4 = R^5 = H$: $R^1 = H$ (**2f**), Me (**2b**);
$R^1 = Me$, $R^2 = R^5 = H$, $R^3–R^4 = CH_2$ (**99**).

Synthetic and natural pentathiepines have various biological activities. The antitumour properties of these compounds were tested. High cytotoxicity of varacin was demonstrated with several types of cancer cells (IC_{50} varies from 1 to 50 nmol litre^{-1}).[87] The cytotoxicity against HCT 116 human colon cancer cells is characterised by $IC_{50} = 0.05$ mg ml^{-1}. Varacin is 100 times more active and 1.5 times less toxic to CHO EM9 tumour cells compared to 5-fluorouracil (the antitumour drug belonging to antimetabolites).[58]

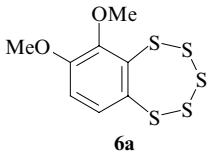
N,N-Dimethyl-5-(methylthio)varacin (**3a**) and synthetic benzopentathiepines **1g** (as hydrochloride), **1h** and **6a** have the cytotoxicity $IC_{50} = 0.26$, 3.2 and 6.1 mg ml^{-1}, respectively, against HeLa53 cells. Pentathiepine hydrochloride **1g** is 10 times more active in these experiments than the corresponding starting arene-1,2-dithiol.[7]



1g·HCl



1h



6a

† The appearance of the previously unknown S_3 species is considered as an important factor in chemical and, which is particularly important, biochemical transformations of pentathiepines, for example, in the explanation of the mechanism of antitumour action of varacin (**2a**). Elimination of S_3 is attributed also to the presence of the side aminoalkyl group, which was found in all natural pentathiepines. The intramolecular attack of the primary or secondary (but not tertiary!) amino group on the S(1) atom of fused pentathiepine is the key step of elimination of the S_3 species.

7-Methylbenzopentathiepine (**1l**) has a thiol-dependent DNA-binding ability. This is the first direct evidence that pentathiepines can act on DNA in physiological conditions.[88] Recently, it has been demonstrated[89] that the nucleophilic attack of thiols leads to a more rapid opening of the pentathiepine ring in 7-methylbenzopentathiepine (**1l**) compared to the analogous reactions with di- and trisulfides. Apparently, this is responsible for the cytotoxic role of natural pentathiepines interacting with endogenous cellular trisulfides. Varacin has an efficient DNA-binding ability both in the presence and in the absence of 2-mercaptoethanol, and this activity increases with increasing concentration of thiol.[87]

Since all natural pentathiepines contain the aminoethyl fragment, the positively charged amino group of pentathiepine antibiotics is presumably favourable for their interactions with DNA.[88,89] Demethylated varacin (**2f**) and *N,N*-dimethyl-5-(methylthio)varacin (**3a**) inhibit protein kinase C with $IC_{50} = 0.5$ and 3.0 mg ml^{-1}, respectively.[59]

Lissoclinotoxin A (**2b**) and lissoclinotoxin B (**99**) are strong antimicrobial drugs, the former compound showing activity toward a number of microorganisms similar to that of cefotaxim.[60] Compounds **2b** and **99** were found to have activity against a fish pathogenic strain similar to that of ampicilin.

Varacin (**2a**), lissoclinotoxin A (**2b**) and benzopentathiepine (**1a**) exhibit high *in vitro* activity against the microorganisms *Candida albicans* and *Bacillus subtilis*.[58,72,73] This activity of the benzopentathiepine system is independent of the presence of an amino group in the side chain. The fungicidal activity of pentathiepinoisothiazole **26** was tested and covered by patents[90–93] for the tomato fungus *Phytophthora infestans*[94] and the fungus *Venturia inaequalis* in infected apple trees.[95] 7-Trifluoromethylbenzopentathiepine (**1u**) at a concentration of 100 ppm provides 100% protection against the apple scab; its 7-dimethylamino analogue **1q**, 100% protection against the cucumber mosaic virus.[96]

Pentathiepines derived from norbornene and its derivatives were proposed as catalysts for vulcanisation of diene rubbers.[97] Benzo- and perhydrobenzopentathiepines were used in photography as additives to emulsion layers or adjacent hydrophilic colloidal layers as antifogging agents;[98] other pentathiepines have found application for the improvement of properties of photographic materials.[99–104] In 2005, Japanese researchers proposed that pentathiepinoindole **40a** be used as a cathodic material for storage batteries.[83]

* * *

In conclusion, it should be noted that 1,2,3,4,5-pentathiepines and 1,2,3,4,5-pentathiepanes are the most stable C_2S_n heterocycles because they are thermodynamically controlled products of numerous sulfurisation reactions. Although only a rather small amount of time has passed since the first synthesis of pentathiepanes (in 1967) and pentathiepines (in 1971) and isolation of natural antibiotics containing the pentathiepine ring from marine organisms (in 1991), a large number of studies on these compounds have been published. These compounds have attracted considerable interest because of their surprising stability, high inversion barriers of the chair-like pentathiepine ring and various biological activities.

The pentathiepine ring can easily be formed with the use of known synthetic methods; however, these heterocycles are often formed accidentally as a result of quite unexpected transformations of sulfur-containing substrates. Since there are numerous possibilities for both the nucleophilic and electrophilic attack on all five sulfur atoms, the pentathiepine ring can be involved in various chemical reactions. Unfortunately, scarce examples were documented for such transformations, the mechanisms of these transformations often remaining unknown. Hence, further investigations in this interesting field of heterocyclic chemistry are required.

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