Benzo-Annelated Cyclic Polysulfides

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Abstract: The preparation, structure, and reactivity of benzo-annelated cyclic polysulfides, which principally contain five- and seven-membered rings, are described together with the chemistry of their related compounds. The stereochemistry of benzopentathiepins and the electrochemistry of benzotrithioles are also discussed.

Keywords: Benzo-annelated cyclic polysulfides, chalcogen atom, phthalocyanine, stereochemistry, electrochemistry, unstable intermediate.

INTRODUCTION

Since the first benzo-annelated cyclic polysulfide, benzopentathiepin, was reported by Fehér in 1971 (Chart **1**) [1], there have been many reports of its derivatives regarding synthesis, structure, biochemical activity, reactivity, and electrochemical property [2]. Particularly, the finding of *Valacin,* which is the first naturally obtained benzopentathiepin [3], is an extremely important result because not only the structure and the bioactivity are interesting [4], but also because benzopentathiepin is a rare example of a substance that was artificially synthesized before its related molecule was obtained naturally.

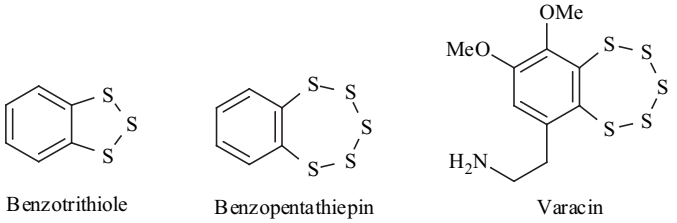

Chart 1.

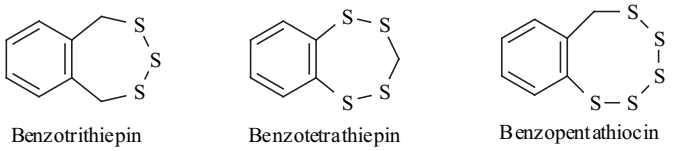

Chart 2.

In this short review, we describe i) preparation of benzo-annelated cyclic polysulfides, ii) electrochemical properties of benzotrithiole and related derivatives, and iii) conformational analyses, optical activities, and biochemical properties of benzopentathiepins. However, compounds bearing several polysulfide-ring-systems containing the methylene group, such as benzo[1,2,3]trithiepin, benzo [1,2,4,5]tetrathiepin, and benzo[1,2,3,4,5]pentathiocin and other saturated ring systems, are not dealt with in this review (Chart **2**).

To explain molecular structure, specific nomenclature is used for the benzo-annelated cyclic polysulfides that indicates the ring size by the following suffixes: three-membered ring (-iren); four-membered ring (-ete); five-membered ring (-ole); six-membered ring (-in); seven-membered ring (-epin); eight-membered ring (-ocin); nine-membered ring (-onin); and ten-membered ring (-ecin). The suffix is used when the ring system is fused to one or more unsaturated C-C double bonds.

PREPARATION OF BENZO-ANNELATED CYCLIC POLYSULFIDES

In benzo-annelated cyclic polysulfides, the five-membered and seven-membered ring systems seem to be more stable than other ring systems do. As a result, until now, most studies concerned five- and seven-membered cyclic polysulfides. It seems that the five-membered ring system, benzotrithiole, is significant for its electrochemical properties, while the seven-membered ring system, benzopentathiepin, is important for its biochemical activities. In contrast, reports of stable compounds concerning the three, four, six, and larger ring systems are rare. According to the report by Greer *et al.*, a relationship exists between stability and ring size [5]. They estimated the structure, reactivity, and stability of benzo-annelated cyclic polysulfides with computational methods, and explained that odd-membered *o*-$C_6H_4S_x$ rings (x = 1-8) have higher stability than even-membered rings do. However, the three-membered ring (x = 1) is an exception because its large steric strain makes it unstable. Their results also show that the five and seven-membered rings are more stable compared

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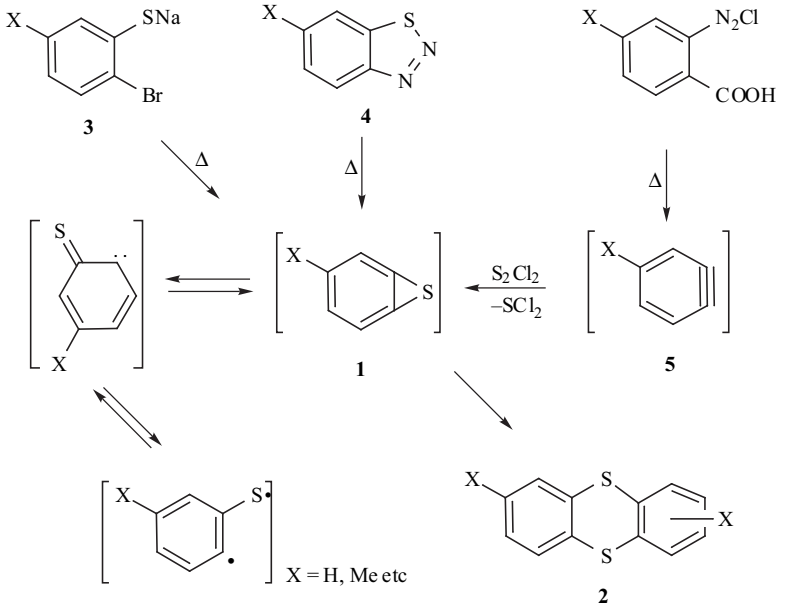


Scheme 1.

with the other ring systems. To characterize the cyclic polysulfides, we will divide the molecules according to ring system size.

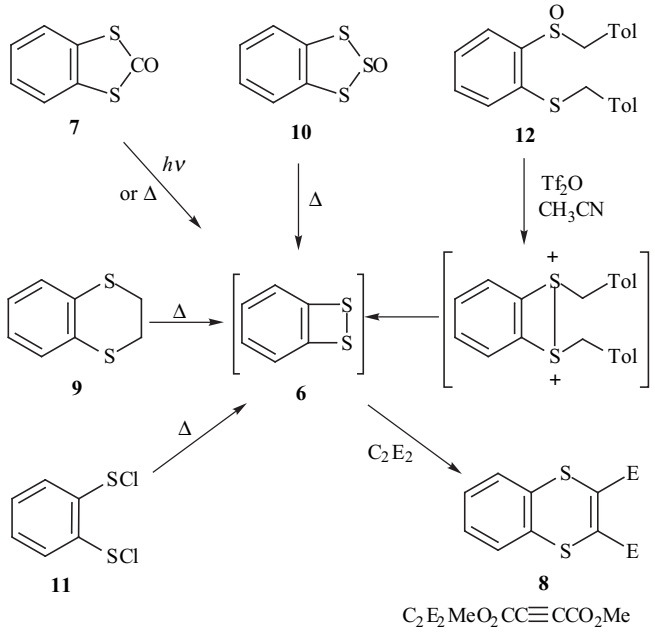
BENZOTHIIREN (THREE-MEMBERED RING)

The smallest benzo-annelated cyclic sulfide is benzothiiren (**1**), which has been described as an intermediate for preparation of thianthrene (**2**) from sodium *o*-bromobenzenethiolate (**3**), benzothiadiazole (**4**), or benzyne (**5**) (Scheme **1**) [6-9]. However, it has not yet been isolated in a stable form. Although there are several arguments about the existence of benzothiiren [10,11], it should be acceptable as an intermediate.

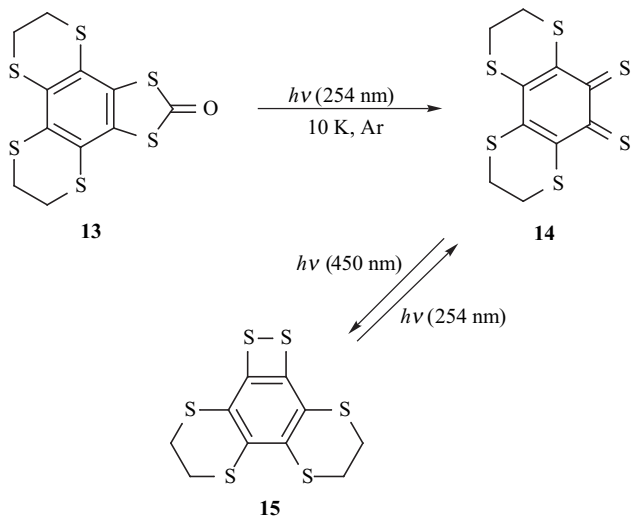
Benzoseleniren, the selenium analogue of benzothiiren, was briefly mentioned as an intermediate in the reaction of benzyne and selenium. However, the possibility of its existence is predicted as being low [9b,12].

BENZODITHIETE (FOUR-MEMBERED RING)

There are many reports of dithiete (not fused to the benzene ring) and related compounds, and the chemistry of dithiete and benzodithiete has been reviewed in detail [13]. Benzodithiete (**6**) is an intermediate of i) photolysis of benzo[1,3]dithiole-2-one (**7**) [14], ii) thermolysis of benzo[1,3]dithiole-2-one (**7**), 2,3-dihydrobenzo[1,4]dithiin (**9**), benzo[1,2,3]trithiole 2-oxide (**10**) [15], and 1,2-*bis*(chlorosulfenyl)benzene (**11**) [16], and iii) decomposition



Scheme 2.



13 **14** **15**

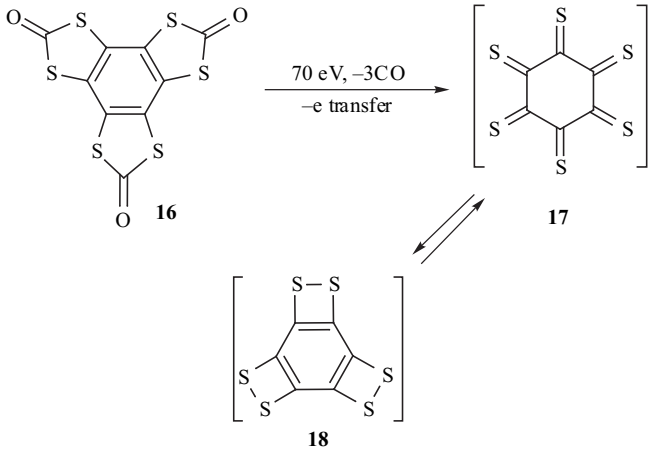
Scheme 3.

of the dication derived from 1-(4-methylbenzylsulfinyl)-2-(4-methylbenzylthio)benzene (**12**) (Scheme **2**) [17]. The benzodithiete (**6**) reacts with DMAD to produce benzo[1,4] dithiin derivative (**8**). Methylbenzodithiete [15] and tetrafluorobenzodithiete [16] were similarly generated with thermolysis of the corresponding benzo[1,3]dithiole-2-one.

Photolysis of 4,5,6,7-*bis*(ethylenedithio)benzo[1,3] dithiole-2-one (**13**) at 10 K under Ar gave the *o*-benzoquinon derivative (**14**), which isomerized to the corresponding benzodithiete (**15**) by 450 nm light irradiation (Scheme **3**) [18].

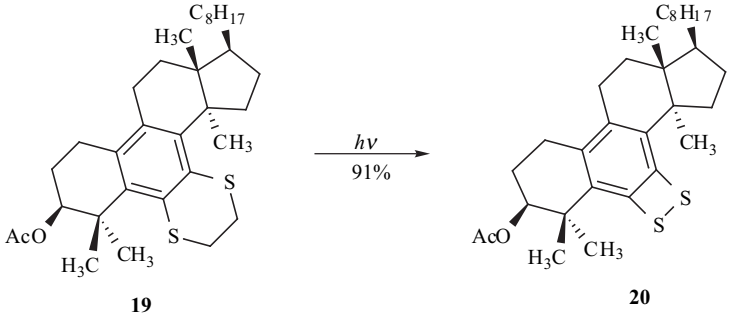
A species, benzohexathione (**17**) or its valence tautomer benzo[1,2-*c*;3,4-*c'*;5,6-*c''*]*tris*[1,2]dithiete (**18**), was generated from benzo[1,2-*d*;3,4-*d'*;5,6-*d''*]*tris*[1,3]dithiole-2-one (**16**) by electron beam irradiation (Scheme **4**) [19].

Only one example of the isolation of stable benzo[1,2] dithiete was reported (Scheme **5**). Benzo[1,2]dithiete (**20**) was obtained as yellow crystals by photolysis of the corresponding dithiin (**19**) in a heptane solution at –20 °C using a medium-pressure mercury lamp [20]. To stabilize benzodithiete, steric protection should be essential.



16 **17** **18**

Scheme 4.



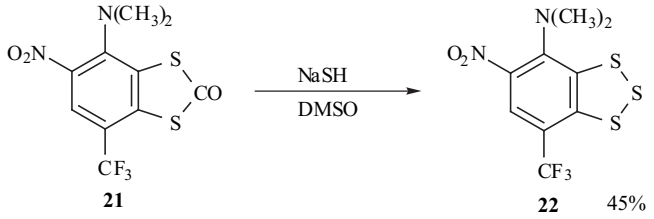
19 **20**

Scheme 5.

Benzodiselenete is briefly mentioned as an intermediate in the reaction of benzyne and selenium [9b].

BENZOTRITHIOLE (FIVE-MEMBERED RING)

There are no reports of benzotrithiole without substituents because it is very unstable. The first report of benzotrithiole (**22**) was by Rasheed in 1980 (Scheme **6**) [21]. The molecule, which was stabilized by two electron-withdrawing substituents, was prepared by the reaction of benzo[1,3]dithiole-2-one (**21**) with NaSH.



21 **22** 45%

Scheme 6.

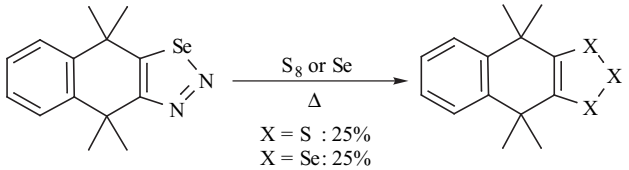
Although the polysulfide ring does not fuse to the benzene ring, the trithiole derivative (**24**) containing a C-C double bond in the five-membered ring was reported by Ando *et al.* (Scheme **7**) [22]. They prepared the compound by thermolysis of the corresponding selenadiazole (**23**) in the presence of sulfur, and a similar reaction with selenium gave a triselenole derivative.

The first benzotriselenole (**26**) was obtained by the thermal reaction of tribenzo[*b,e,h*][1,4,7]trimercuronin (**25**) with selenium (Scheme **8**) [23]. The product was determined by mass spectrometry and elemental analysis.

On treatment of benzo[1,2-*d*;4,5-*d'*]*bis*[1,3]dithiole-2,6-dithiones (**27**) with sulfur in liquid ammonia at room temperature, trithiolo[5,4-*h*]benzopentathiepins (**28**), which are the first example of a molecule with two polysulfide rings, were obtained in high yields (Scheme **9**) [24a]. When the alkoxy groups do not exist on the benzene ring of benzo[1,2-*d*;4,5-*d'*]*bis*[1,3]dithiole-2,6-dithione, the corresponding polysulfide derivative is not obtained at all.

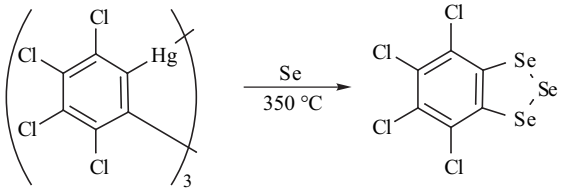
1,4-Dialkyltetrabromobenzene was treated with sulfur in liquid ammonia at 120 °C in an autocleave to afford trithiolo[5,4-*h*]benzopentathiepin (**29**) and benzo[1,2-*d*;4,5-*d'*]*bis*[1,2,3]trithiole (**30**) (Scheme **10**) [24b]. If the reaction temperature is under 100 °C, the reaction gives no product.

On treatment of hexamercaptobenzene with methyl lithium and then sulfur dichloride, the compounds with three trithiole rings, benzo[1,2-*d*;3,4-*d'*;5,6-*d''*]*tris*[1,2,3]



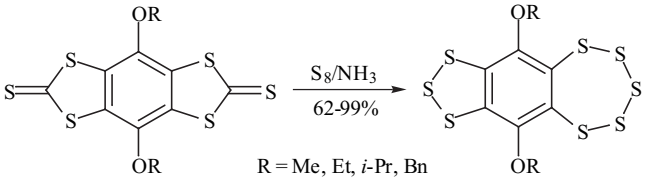
23 **24**

Scheme 7.



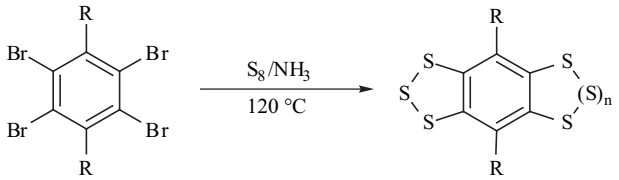
25 **26**

Scheme 8.



27 **28**

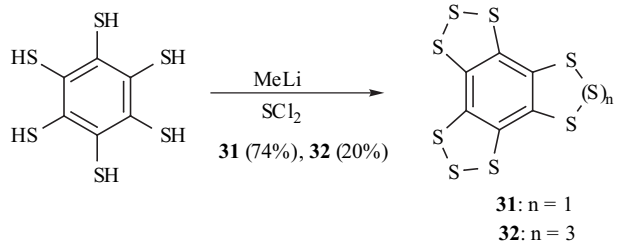
Scheme 9.



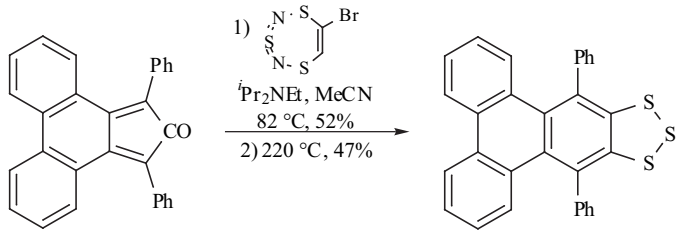
R = Me: **29** (70%), **30** (11%)
Et : **29** (64%), **30** (27%)

29: n = 3
30: n= 1

Scheme 10.



Scheme 11.



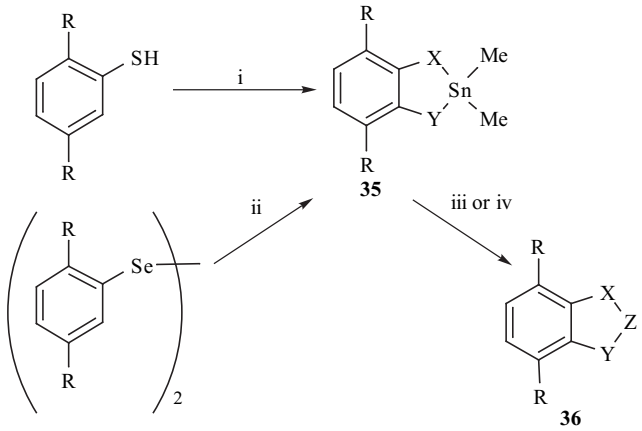
Scheme 12.

trithiole (**31**), and one pentathiepin and two trithiole rings, [3,4-*d*;5,6-*d'*]*bis*[1,2,3]trithiolo[1,2-*h*]benzopentathiepin(**32**), were obtained in good yields (Scheme **11**) [25].

The trithiole derivative (**34**) containing a triphenylene skeleton was prepared in moderate yield *via* Diels-Alder reaction of the compound (**33**) and subsequent thermal decomposition of the product (Scheme **12**) [26].

From the time when the ortho-directed lithiation of thiophenol was reported by Martin [27a], Block [27b], and Smith [27c] in 1989, a new procedure for preparation of benzo-annelated cyclic polysulfides was developed and advanced, and the process was applied to the selenium derivatives (Scheme **13**).

4,7-Disubstituted 2,2-dimethylbenzo[1,3,2]dichalcogenastannoles (**35**), which are a synthetic equivalent of unstable 1,2-benzenedichalcogenols, were prepared in moderate yields by a sequence of ortholithiation-chalcogenation and dimethyltin protection (Table **1**) [28]. Transformation into the corresponding trichalcogenoles (**36**) was successfully performed by the reaction of the stannoles (**35**) with electrophiles containing one sulfur or selenium unit (Table



i, a) TMEDA, *n*-BuLi, hexane, b) S_8 or Se, c) Me_2SnCl_2

ii, a) $LiAlH_4$, THF, b) H^+/H_2O, c) TMEDA, *n*-BuLi, hexane, d) S_8 or Se, e) Me_2SnCl_2

iii, a) $SOCl_2$, THF, b) NaI-$HClO_4$, THF/H_2O

iv, a) $SeOCl_2$, THF, b) TMSOTf, THF, c) SmI_2, THF

Scheme 13.

Table 1. Preparation of Benzodichalcogenastannoles

R	X	Y	Products	Yield (%)	R	X	Y	Products	Yield (%)
i-Pr	S	S	**35a**	70	Et	Se	Se	**35f**	18
i-Pr	S	Se	**35b**	70	MeO	S	S	**35g**	45
i-Pr	Se	Se	**35c**	64	MeO	S	Se	**35h**	49
Et	S	S	**35d**	28	MeO	Se	Se	**35i**	31
Et	S	Se	**35e**	23					

Table 2. Preparation of Benzotrichalcogenoles

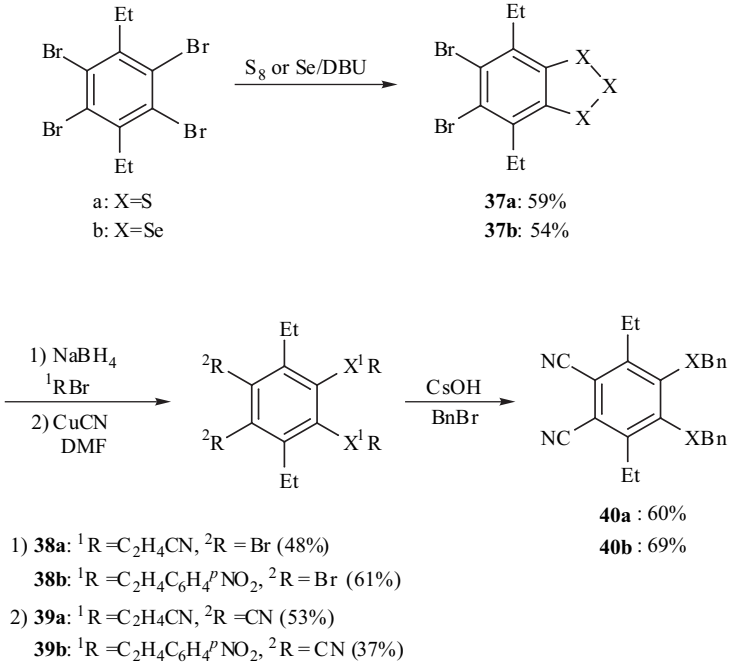
R	X-Z-Y	Products	Yield (%)	R	X-Z-Y	Products	Yield (%)
i-Pr	S-S-S	**36a**	96	Et	S-Se-S	**36j**	85
i-Pr	S-S-Se	**36b**	86	Et	S-Se-Se	**36k**	85
i-Pr	Se-S-Se	**36c**	91	Et	Se-Se-Se	**36l**	53
i-Pr	S-Se-S	**36d**	90	MeO	S-S-S	**36m**	82
i-Pr	S-Se-Se	**36e**	74	MeO	S-S-Se	**36n**	84
i-Pr	Se-Se-Se	**36f**	74	MeO	Se-S-Se	**36o**	79
Et	S-S-S	**36g**	78	MeO	S-Se-S	**36p**	71
Et	S-S-Se	**36h**	78	MeO	S-Se-Se	**36q**	85
Et	Se-S-Se	**36i**	77	MeO	Se-Se-Se	**36r**	85

2). By this procedure, trithiole derivatives containing naphthalene or phenanthrene were also obtained [28f].

Benzo[1,2,3]trichalcogenoles with two bromine atoms on the benzene ring, dibromobenzo[1,2,3]trichalcogenoles (**37**) [chalcogen: S and Se], were prepared by treating 1,4-diethyltetrabromobenzene with elemental sulfur or amorphous selenium in DBU for 24 h (Scheme **14**) [29]. The structures of **37** were determined by X-ray crystallographic analysis.

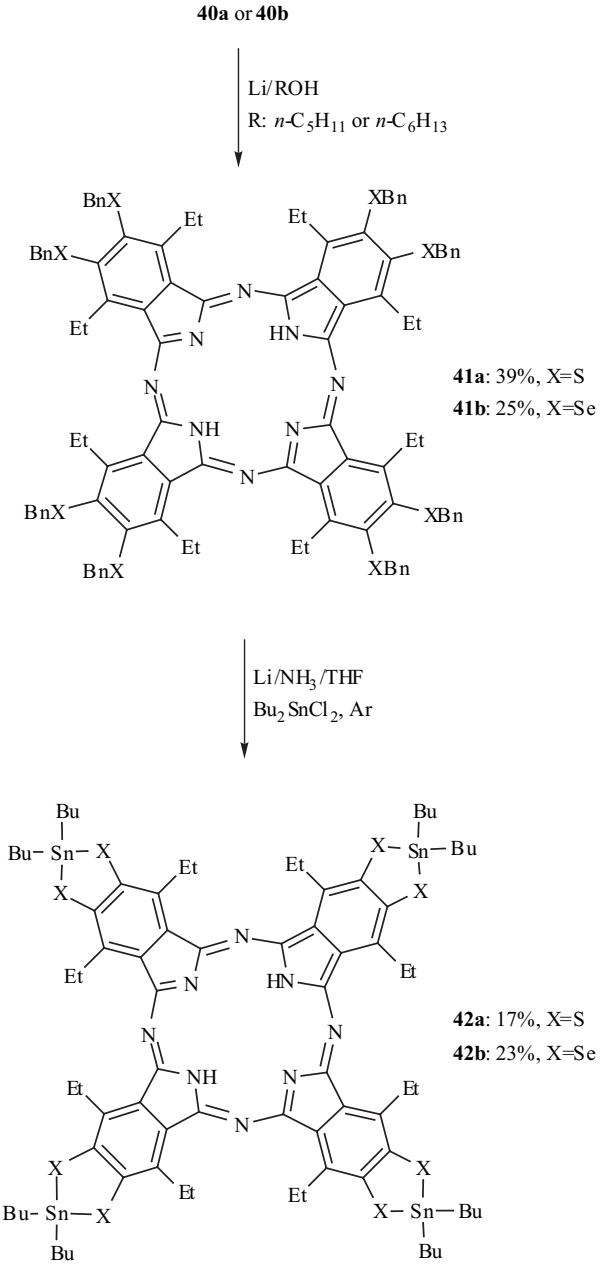
The compounds **37** were converted to phthalocyanine derivatives (**41**) with eight benzylchalcogeno substituents *via* compounds **38**, **39**, and **40** (Scheme **15**) [29]. To prepare phthalocyanines modified peripherally, phthalocyanine (**41**) was treated with lithium in THF/liquid ammonia and then dibutyltindichloride, which produces new functionalized phthalocyanine (**42**).

To prepare phthalocyanine with the trithiole ring, reductive removal of four *o*-xylylene groups from tetrakis(*o*-xylylenedithio)phthalocyanines (**43**) was performed with lithium/THF/ammonia at –78 °C (Scheme **16**) [30]. The octathiolate anions generated were then reacted with elemental sulfur to give new phthalocyanines (**44**) with one pentathiepin and three trithiole rings. However, the product could not be isolated from the compound with higher molecular weight. Desulfurization and ring contraction reactions of the phthalocyanines (**44**) gave phthalocyanines (**45**) with four trithiole rings. The absorption of the Q-band of **43** was observed at around λ_{max} = 770 nm in the UV-vis spectra, while that of **45** was found at around a relatively blueshifted region. When the UV-vis spectrum for **45** was measured in concentrated sulfuric acid, the λ_{max} value of the Q-band was 887 nm (log ε = 4.5), which suggests that the positive charge generated on **45** strongly affects the π-



Scheme 14.

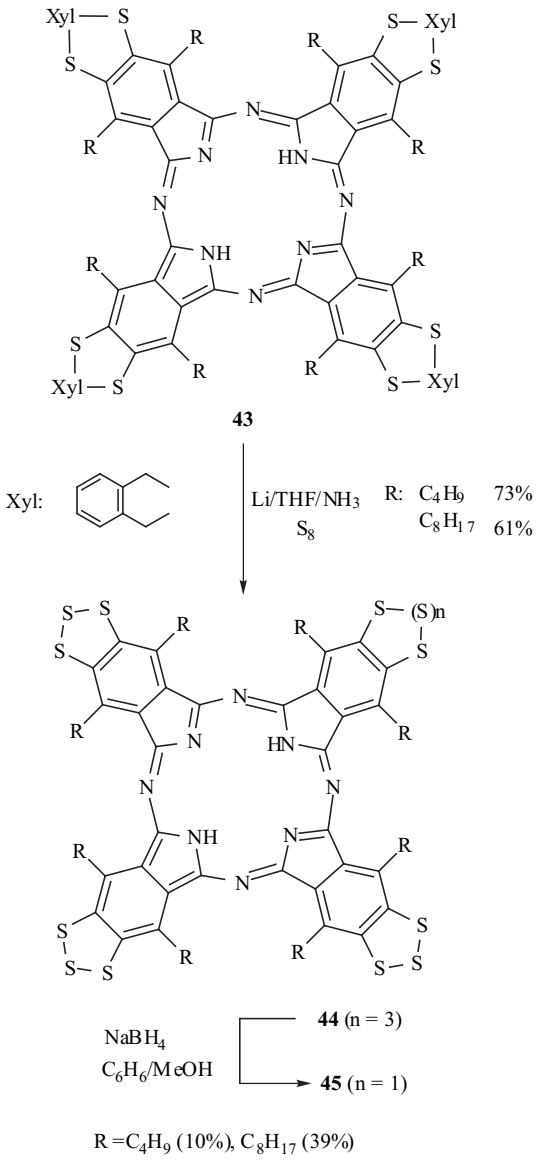
conjugation of the phthalocyanine skeleton. The ESR spectrum was observed as one broadening signal on treatment of **45** with $SbCl_5$.



Scheme 15.

BENZOTETRATHIIN (SIX-MEMBERED RING)

Reports of polysulfide containing a benzo-annelated six membered-ring are rare, and benzo[1,2,3,4]tetrathiin is only mentioned as an intermediate [4h]. Recently, 6,8-dimethoxybenzotetrathiin (**46**) was prepared by a procedure similar to the process for benzotrithioles [31]. The reaction of disubstituted dithiastannole (**35g**) with S_2Cl_2 in THF gave tetrathiin (**46**) (Scheme **17**), and the structure was determined by X-ray crystallography. The ring size of the product seems to be affected by the solvent and the sulfurization reagent, which gave benzotrithiole (**36m**), benzotetrathiin (**46**), and benzopentathiepin (**47**).

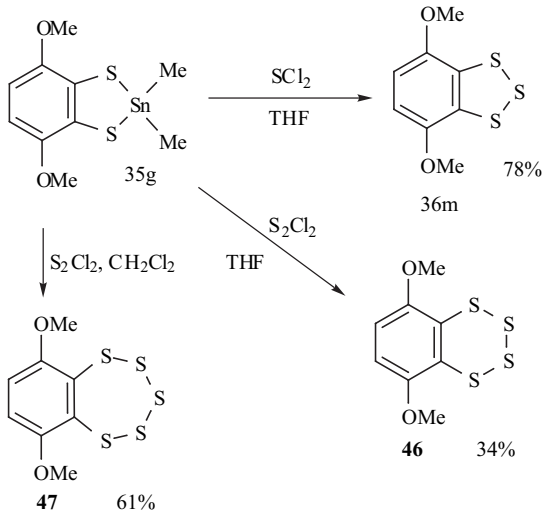


Scheme 16.

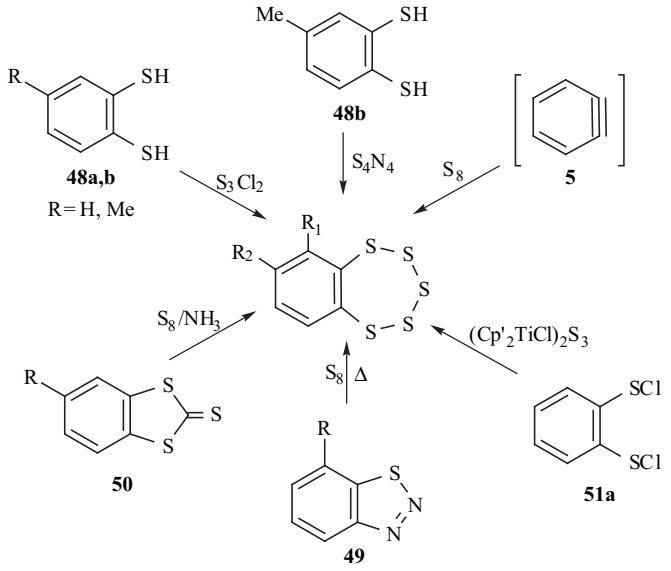
BENZOPENTATHIEPIN (SEVEN-MEMBERED RING)

Benzopentathiepin and analogous compounds are interesting molecules because of their structure, reactivity, metabolism, and biological activities. Benzopentathiepins were first prepared by Fehér upon treatment of *o*-benzenedithiols (**48a**,**b**) with S_3Cl_2 (Scheme **18**) [1,32]. Since then, several procedures for preparation of the compound have been reported by Chenard [33], Sato [34], Nakayama [9b], Steudel [35], and Rees [36].

Benzopentathiepins were obtained by heating the corresponding benzo[1,2,3]thiadiazoles (**49**) with sulfur in decalin at 160-185 °C [33]. The procedure was discovered and developed by Chenard and co-workers. Benzo[1,2,3] thiadiazoles with H, Cl, CF_3, OMe, NMe_2, or Br as a substituent gave benzopentathiepins in good yields; the addition of DABCO to the reaction increases the yields.



Scheme 17.



Scheme 18.

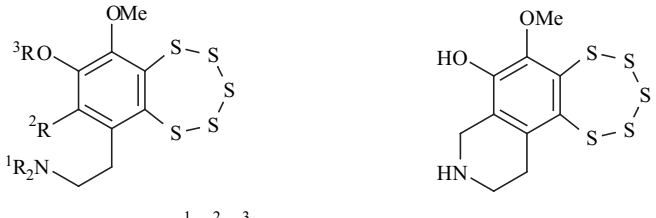
Synthesis of 7-substituted benzopentathiepins was performed on treatment of benzo[1,3]dithiole-2-thione (**50**) with sulfur and liquid ammonia at room temperature [34].

Benzyne (**5**) generated by the usual procedures was reacted with elemental sulfur to produce benzopentathiepin in low yield [9b].

The insertion of three sulfur atoms into 1,2-*bis*(chlorosulfenyl)benzene (**51a**) proceeded on treatment with *bis*(*bis*(pentamethylcyclopentadienyl)chlorotitanium) trisulfide to give benzopentathiepin in good yield [35].

Benzopentathiepin was also formed by the reaction of tetrasulfur tetranitride (S_4N_4) with benzene-1,2-dithiol (**48b**) under xylene reflux [36].

The first naturally occurring benzopentathiepins, *Varacin*, *Lissoclinotoxin A*, *Lissoclinotoxin B*, and *N,N-dimethyl-5-(methylthio)varacin*, have antimicrobial and antifungal properties, and *Varacin* is highly toxic toward human colon cancer (Chart **3**) [3]. The total synthesis of *Varacin* was performed by Behar [4a], Davidson [4b,4f], and Still [4h].



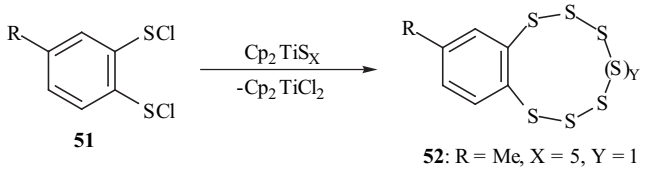
Lissoclinotoxin A (^{1}R,^{2}R,^{3}R = H)
Methylthiovaracin (^{1}R,^{3}R = H, ^{3}R = SMe)

Lissoclinotoxin B

Chart 3.

LARGER SIZED RINGS

Steudel has reported benzo-annelated cyclic polysulfides with nine-membered, ten-membered and twelve-membered rings (Scheme **19**) [35,37]. Titanocene polysulfide has been used as a sulfur transfer reagent, which reacted with 1,2-*bis*(chlorosulfenyl)benzene (**51**) to produce the corresponding cyclic polysulfides (**52**), (**53**) and (**54**). The structure of benzoheptathionin (**52**) was determined by X-ray crystallography.



51

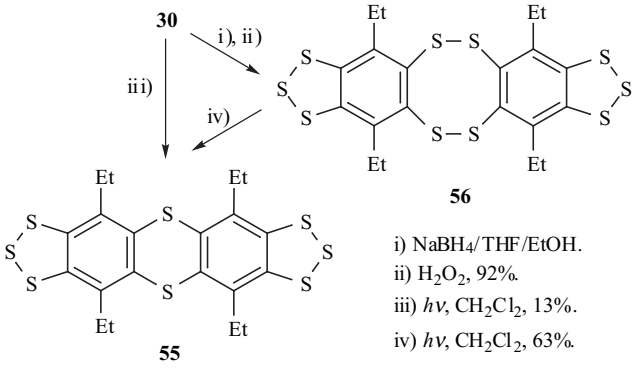
52: R = Me, X = 5, Y = 1
53: R = H, X = 6, Y = 2
54: R = H, X = 8, Y = 4

Scheme 19.

REACTIVITY, ELECTROCHEMICAL PROPERTY AND CONFORMATION ANALYSIS

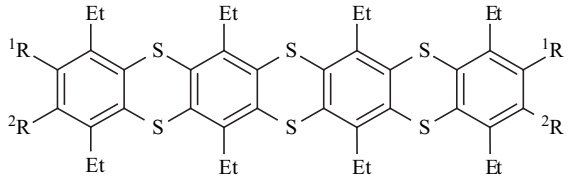
Photolysis

Irradiation of diethylbenzopentathiepin in dichloromethane gave benzotrithiole, dibenzotetrathiocin, and thianthrene by way of consecutive desulfurization, dimerization, and ring contraction [38,39]. Photolysis of benzobistrithiole (**30**) produced thianthrene (**55**) with two trithiole rings in low yield (Scheme **20**). In contrast, irradiation of tetrathiocin (**56**) under similar conditions produced thianthrene (**55**) in good yield.



Scheme 20.

Photolysis of substituted thianthrene derivatives with the trithiole ring produced *bis*(ethylenedithio)hexathiaheptacene (**57**) and *tetrakis*(octylthio)hexathiaheptacene (**58**) (Chart **4**).



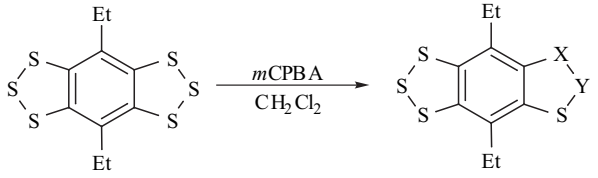
57: ^1R, $^2R = SCH_2CH_2S$, **58**: $^1R = {}^2R = SC_8H_{17}$

Chart 4.

Oxidation

Benzobistrithiole (**30**) was oxidized with *m*CPBA to produce the corresponding 1-oxide (**59**) and 2-oxide (**60**) (Scheme **21**) [40]. By irradiation with UV-Vis light, 2-oxide (**59**) isomerizes to 1-oxide (**60**), quantitatively.

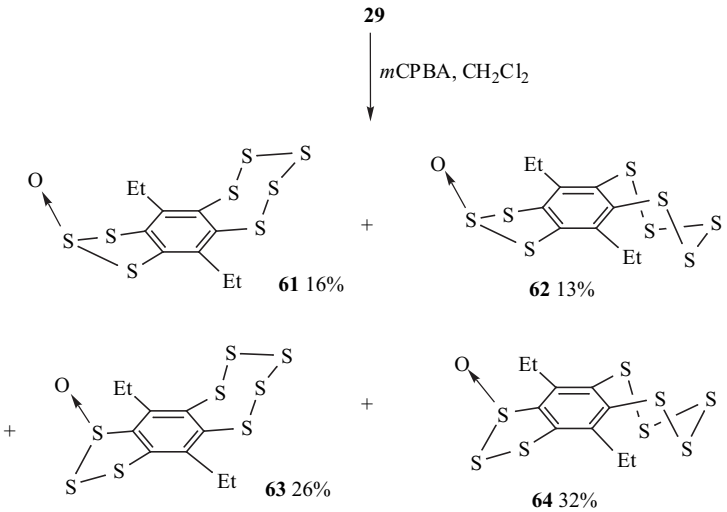
To compare the reactivity between the trithiole and pentathiepin rings, trithiolo[5,4-*h*]benzopentathiepin (**29**) was oxidized with *m*CPBA to give the corresponding trithiole 2-oxides (**61**) and (**62**), and trithiole 1-oxides (**63**) and (**64**). The structures of the products were determined by X-ray crystallographic analysis (Scheme **22**) [41].



30

59: X = SO, Y = S (68%)
60: X = S, Y = SO (18%)

Scheme 21.



Scheme 22.

In the structures, the oxygen atoms coordinated with the sulfur atom of **61**, **62**, **63**, and **64** are located on the axial position of the trithiole ring. The oxygen atoms of **61** and **63** exist on the *syn* side of the pentathiepin ring, and those of **62** and **64** orient to the *anti* side of the pentathiepin ring.

Several Reactions of Benzopentathiepin

Several reactions of benzopentathiepin gave related sulfur heterocycles (Chart **5**). In the presence of aluminum chloride, benzopentathiepin reacts with substituted benzenes in a Friedel-Crafts type reaction to produce the corresponding thianthrene derivatives (**65**) [42a]. Reaction with norbornene in the presence of triethylamine in DMF gave cyclo-adduct (**66**) [42b]. By reaction with simple alkenes in the presence of boron trifluoride, benzopentathiepin was transformed to unsymmetrically substituted 1,2,5-benzotrithiepin (**67**), which gave the corresponding monoxide (**68**) with oxidation [42c].

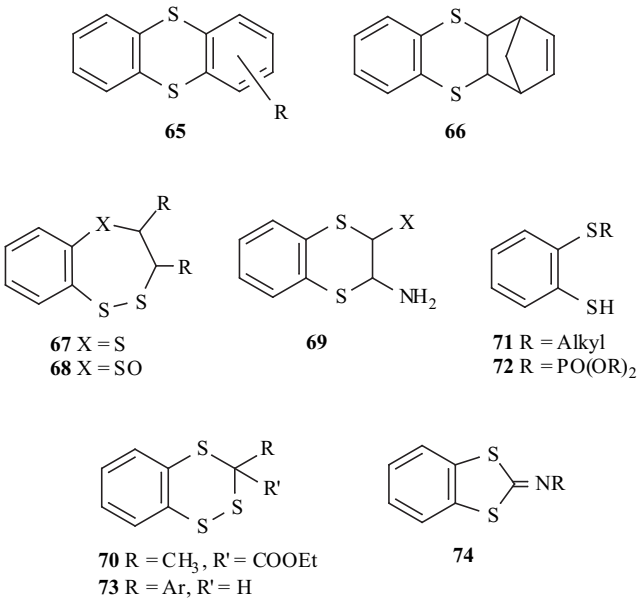
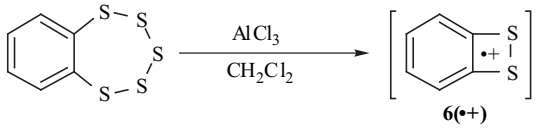


Chart 5.

Various active methylene compounds react with benzopentathiepin in the presence of triethylamine or sodium methoxide to give benzo[1,4]dithiins (**69**) [42d] and benzo[1,2,4]trithiins (**70**) [42e]. The reaction with Grignard reagents gave 2-alkylthio- and 2-arylthio benzenethiols (**71**) [42f]. Treatment with trialkyl phosphates produced thiophosphonates (**72**) [42g]. Benzopentathiepin reacted with benzylic phosphonium salts and sodium hydride to produce trithiins (**73**) [42h]. 2-Iminobenzo[1,3]dithioles (**74**) were prepared from benzopentathiepin and isothiocyanates in the presence of triethyl amine [42i]. Phenyl isoselenocyanates gave the same product.

Electrochemical Properties

Radical cations of benzo-annelated cyclic polychalcogenides are known in the four- and five-membered ring systems. A benzodithiete radical cation **6(•+)** was generated on treatment of benzopentathiepin with $AlCl_3$ and detected with EPR spectroscopy although it could not be isolated in a stable form (Scheme **23**) [43,44].



Scheme 23.

Five-membered rings containing trisulfide or triselenide bonds could generate corresponding radical cations (Chart **6**). The radical cation (**75**) derived from trithiole was first isolated by Cameron [45] although it was not a benzotrithiole derivative. The chemistry of benzo-annelated triselenole radical cations (**76**) was started by Wolmershäuser [46], and the radical cation (**77**) and dications (**78**) and (**79**) derived from the compound with two or three trithiole rings were reported by Fanghänel [25].

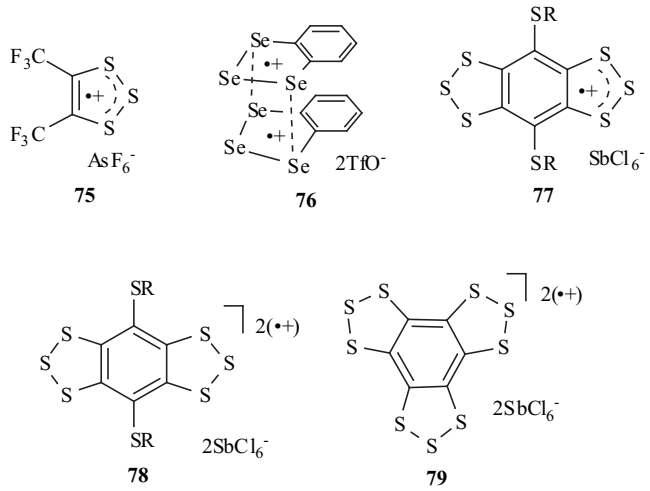
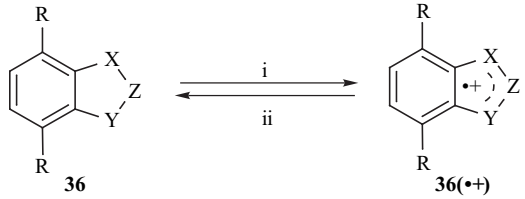


Chart 6.

Several novel trichalcogenolium radical cation salts **36(•+)** were readily isolated in the one-electron oxidation of trichalcogenoles (**36**) with one equivalent $NOPF_6$ in ether-MeCN (Scheme **24** and Table **3**) [28]. The EPR spectra of the solution showed the presence of triplet peaks and a broad singlet peak attributable to trichalcogenolium radical cations (Table **4**). The peak splitting suggests a partially spin delocalized system over both the benzene and trichalcogenole rings. Interestingly, on treatment with samarium (II) iodide, the radical cation salts undergo one-electron reduction to give trichalcogenoles quantitatively (Scheme **24** and Table **3**).



i, $NOPF_6$, Et_2O/MeCN; ii, SmI_2, THF

Scheme 24.

Benzobistrithiole (**30**) was oxidized using concentrated D_2SO_4, leading to generation of the radical cation **30(•+)**, which was verified by EPR spectroscopy (Scheme **25**) [47]. The radical cation **30(•+)** in the solution was further oxidized to produce dication **30(2+)**, which was determined

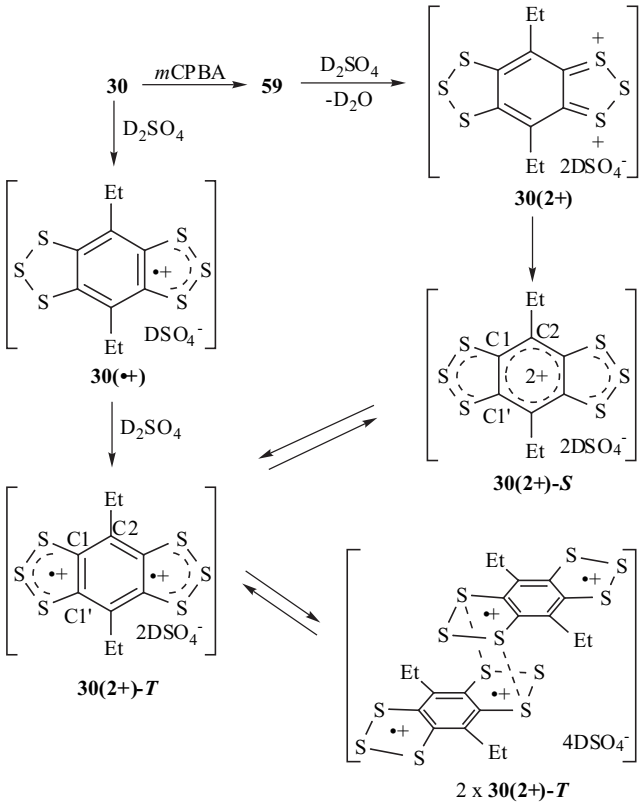
Table 3. Preparation and Reduction of Benzotrichalcogenole Radical Cations

R	X-Z-Y	Products	i), Yield (%)	R	X-Z-Y	Products	ii), Yield (%)
i-Pr	S-S-S	**36(•+)a**	95	*i*-Pr	S-S-S	**36a**	92
i-Pr	Se-S-Se	**36(•+)c**	92	*i*-Pr	Se-S-Se	**36c**	quant.
i-Pr	Se-Se-Se	**36(•+)f**	99	*i*-Pr	Se-Se-Se	**36f**	94
Et	S-S-S	**36(•+)g**	quant.	Et	S-S-S	**36g**	quant.
Et	Se-S-Se	**36(•+)i**	quant.	Et	Se-S-Se	**36i**	quant.
Et	Se-Se-Se	**36(•+)l**	97	Et	Se-Se-Se	**36l**	quant.
MeO	S-S-S	**36(•+)m**	94	MeO	S-S-S	**36m**	94
MeO	Se-S-Se	**36(•+)o**	quant.	MeO	Se-S-Se	**36o**	quant.
MeO	Se-Se-Se	**36(•+)r**	99	MeO	Se-Se-Se	**36r**	94

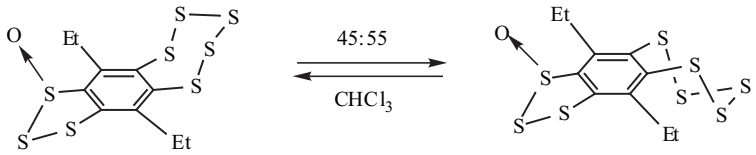
Table 4. ESR Parameters of Benzotrichalcogenole Radical Cations

Products	g	Hfc (Hz)	Products	g	Hfc (Hz)	Products	g	Hfc (Hz)
36(•+)a	2.012	0.106	**36(•+)g**	2.012	0.109	**36(•+)m**	2.012	0.081
36(•+)c	2.033	-	**36(•+)i**	2.033	-	**36(•+)o**	2.032	-
36(•+)f	2.058	-	**36(•+)l**	2.055	-	**36(•+)r**	2.057	-

by NMR spectroscopy. The dication **30(2+)** was also prepared by treating trithiole 1-oxide (**59**) with concentrated D_2SO_4 and was verified by ^1H and ^{13}C-NMR. The EPR signal of **30(2+)** generated from trithiole 1-oxide (**59**) was observed in the solution, which implies that singlet-state dication **30(2+)-*S*** isomerizes to triplet-state dication **30(2+)-**



Scheme 25.



63 **64**

Scheme 26.

T, and that two molecules of **30(2+)-*T*** further form a spin pair at one trithiole ring with sufficient distance between the two radical centers.

Conformational Analysis and Asymmetry

The ^{1}H-NMR spectra of *Varacin* and *Lissoclinotoxin A* showed unexpectedly complex signals for benzylic protons of the side-chain [4]. The signal complexity is the result of a high-energy barrier for inversion of the pentathiepin ring, which induces asymmetry in the molecule.

The trithiole 2-oxides (**61**) and (**62**) and the trithiole 1-oxides (**63**) and (**64**) were stable in the crystalline form [41]. However, they were found to isomerize to each other slowly in a $CHCl_3$ solution at room temperature (Scheme **26**). The equilibrium ratio of **61** and **62** was 55:45, and that of **63** and **64** was 45:55. Because the pyramidal inversion of the sulfinyl group has been known not to proceed at room temperature, the isomerizations should proceed *via* the inversion of the pentathiepin rings.

To verify the inversion energy of the pentathiepin ring experimentally, the isomerization was monitored by ^{1}H-NMR spectroscopy and the results were plotted (Fig. **1**). Table **5** lists the calculated kinetic parameters of these compounds. The Eyring treatment of the rate constants obtained at those temperatures enabled us to calculate the activation parameters of the isomerization of these compounds (Fig. **2**). Table **5** lists all the activation parameters, $\Delta G^{\neq}$, $\Delta H^{\neq}$, and $\Delta S^{\neq}$. The values of $^{298}\Delta G^{\neq}$ are about 24.0 kcal/mol, suggesting that the inversion of the

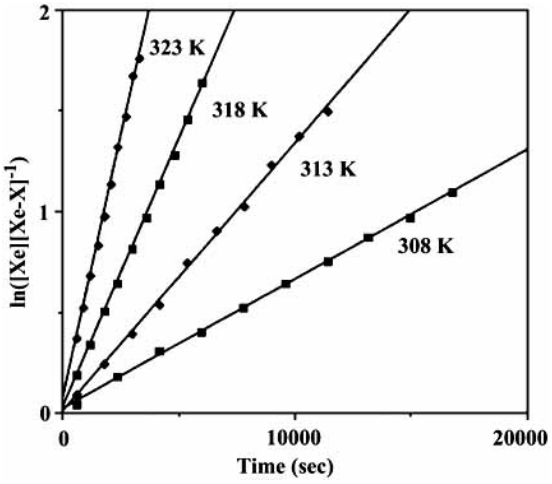


Fig. (1). The representative kinetic data for the inversion of the pentathiepin ring of **64a**; [Xe]: Equilibrium concentration; [Xe-X]: Concentration as a function of time.

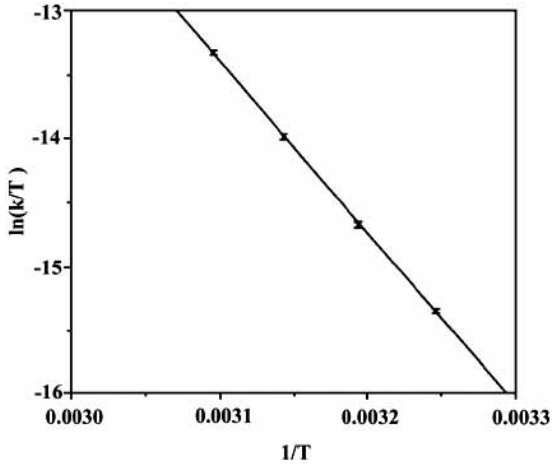


Fig. (2). Eyring treatment with standard deviation for the inversion of the pentathiepin ring of **64a**.

Table 5. Kinetic and Thermodynamic Parameters

	61	62	63	64
^{303}k (sec^{-1})	$(4.71\pm1.17)\times10^{-5}$	$(3.89\pm0.18)\times10^{-5}$	-	-
^{308}k (sec^{-1})	$(7.79\pm0.95)\times10^{-5}$	$(8.53\pm0.31)\times10^{-5}$	$(6.38\pm0.35)\times10^{-5}$	$(6.42\pm0.13)\times10^{-5}$
^{313}k (sec^{-1})	$(1.62\pm0.24)\times10^{-4}$	$(1.84\pm0.36)\times10^{-4}$	$(1.24\pm0.06)\times10^{-4}$	$(1.32\pm0.03)\times10^{-4}$
^{318}k (sec^{-1})	$(3.15\pm0.54)\times10^{-4}$	$(3.81\pm0.50)\times10^{-4}$	$(2.33\pm0.05)\times10^{-4}$	$(2.65\pm0.09)\times10^{-4}$
^{323}k (sec^{-1})	$(6.09\pm0.23)\times10^{-4}$	$(6.41\pm0.94)\times10^{-4}$	$(4.64\pm0.20)\times10^{-4}$	$(5.23\pm0.10)\times10^{-4}$
$^{298}\Delta G^{\neq}$ (kcal/mol)	23.8±0.1	23.9±0.1	24.0±0.1	24.1±0.0
$\Delta H^{\neq}$ (kcal/mol)	25.1±1.0	27.0±1.8	25.4±0.7	27.1±0.1
$\Delta S^{\neq}$ (eu)	4.4±3.1	10.3±5.9	4.7±2.2	9.9±0.3

pentathiepin rings of these compounds proceeds very slowly at room temperature. The kinetic and thermodynamic data for benzopentathiepins are closely related to those for saturated pentathiepan derivatives [48].

Because of the slow inversion of the pentathiepin ring, it is possible to isolate unsymmetrically substituted benzopentathiepin as a chiral molecule. Asymmetric oxidation of **29** was performed by a Sharpless reagent [**29**/Ti(O^iPr)$_4$/*R,R*-DET/*t*-BuOOH=1:2:4:4] to produce optically active monoxides **63a** and **64a** (Scheme **27**) [41b,49].

By repeated recrystallization, **63a** and **64a** were each obtained as optically pure yellow crystals. Specific rotation $[\alpha]_D$ was then measured in $CHCl_3$: $[\alpha]_D^{20} = -775°$ (c = 0.204) for **63a** and $[\alpha]_D^{19} = -1364°$ (c = 0.161) for **64a**, and the enantiomeric excess was determined by ^1H NMR using [Eu(hfc)$_3$] as *ee* = 100% for **63a** and *ee* = 98% for **64a**. The configuration of the sulfinyl group of **63a** and **64a** was confirmed by X-ray crystallographic analysis as *R* configuration for both compounds.

Their circular dichroism spectra were then measured in $CHCl_3$ (concentration: 6.46×10^{-5} mol/l). As shown in Fig. (**3**), the circular dichroism spectrum of **63a** shows a positive first Cotton effect at 391 nm, while that of **64a** shows a negative first Cotton effect at 384 nm. Since the configuration of the sulfinyl group of both **63a** and **64a** is *R* configuration, as described above, the different sign of this first Cotton effect should occur from the conformation of the pentathiepin ring. The specific rotation and the circular dichroism spectra of **63a** and **64a** are apparently affected by the conformation of the pentathiepin ring.

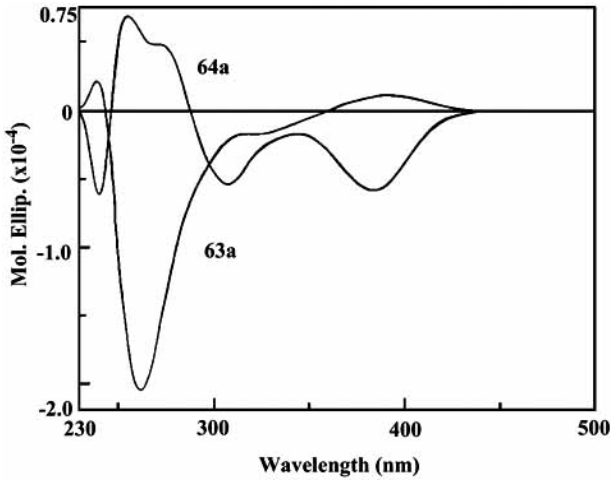
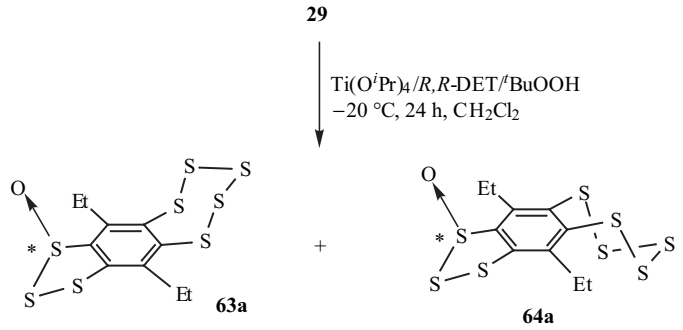


Fig. (3). The circular dichroism spectra of **63a** and **64a** (Concentration: 6.46×10^{-5} mol/L).



29 : Ti(O^iPr)$_4$: *R,R*-DET : ^{t}BuOOH = 1 : 2 : 4 : 4
61+**62** (29%); **63a** (18%); **64a** (23%).

Scheme 27.

BIOLOGICAL ACTIVITY

The naturally occurring benzopentathiepins have some biological activity. However, their biological essentiality and operation in the ascidian itself have not yet been understood. Since these benzopentathiepins contain the skeleton of dopamine, they should be made from dopamine derivatives in the respective organ.

Synthetic and natural benzopentathiepins are active for several microorganisms and mammalian tissues. For instance, *Varacin* exhibits cytotoxicity toward human colon cancer HCT 116 with IC90 = 0.05 g/mL, which is 100 times the activity of 5-fluorouracil in this assay. *Lissoclinotoxin A* [4d], *Lissoclinotoxin B* [4d], and *N,N-Dimetrhyl-5-methylthio-Varacin* [4g] also show biological activity. The synthetic benzopentathiepins, 6,7-dimethoxy-benzopentathiepin, 7-(2-Boc-aminoethyl)benzopentathiepin, and 7-(2-ammoniumethyl)benzopentathiepin chloride, exhibit cytotoxicity with IC50 = 6.1, 3.2, and 0.26 g/mL, respectively, toward HeLa53 cells [50]. These results show that the aminoethyl group of *Varacin* derivatives is significant for their biological activity [50]. In contrast, 7-methylbenzopentathiepin has DNA-cleaving ability [4i,4j]. This is the first direct evidence that pentathiepins can cleave DNA under physiological conditions; the nucleophilic attack of thiols on 7-methylbenzopentathiepin initiates the DNA cleavage.

CONCLUSION

The chemistry of the benzo-annelated cyclic polychalcogenide has just about been restricted to the five- and seven-membered rings because of the unstability of the rings of other sizes. However, the small-sized mono or disulfide rings are interesting because of their isolation, structure, and reactivity. The benzotrichalcogenoles and related compounds would be significant with respect to the study for organic devices, while the photolysis of benzotrithioles is useful in the preparation of functionalized thianthrene derivatives. Although there have been many reports of benzopentathiepins for preparation and reactions, they will be studied for their biological activities.

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