Synthesis, Structure, and Properties of Pentathiepins

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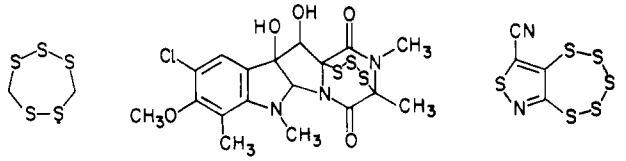
Abstract: A series of aromatic and heteroaromatic fused pentathiepins has been prepared by several methods. The X-ray structure analysis of several of these compounds has been obtained along with other useful characterization data (laser Raman, UV, etc.). Certain benzopentathiepins can be made to disproportionate into sulfur and benzotrithioles. In one case (6-(trifluoromethyl)benzopentathiepin, **5c**), an apparent equilibrium is established with the benzotrithiole and sulfur. The relatively unstable benzotrithioles were identified by GC/MS and UV spectrometry. Steric and electronic factors which control the ring size in benzopolysulfides have been examined, and a few selected reactions of pentathiepins are described.

The past few years have witnessed an ever-increasing interest in the area of organic polysulfides.[2] Particularly intriguing are the cyclic polysulfides which range in complexity from monocyclic molecules such as lenthionine (**1**)[3] to the polycyclic compound sporidesmin E (**2**).[4] Our entry into this area was prompted by

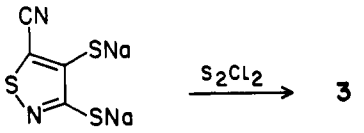


1 **2** **3**

the serendipitous synthesis of 8-cyanoisothiazolopentathiepin (**3**),[5] a compound with a fascinating spectrum of antifungal activity.[5b] Since this initial discovery, we have explored in some detail the synthesis and properties of these unique compounds. We present here our various approaches to aryl and heteroaryl fused pentathiepins. Additionally, since there are frequently problems with structural assignment associated with cyclic polysulfides,[6] we report X-ray structural analyses for several compounds as well as useful spectral data. Finally, we have been concerned with the potential for equilibrating pentathiepins with other size polysulfur rings. This question has been addressed by several groups with regard to the allotropes of elemental sulfur.[7] We find that in some cases, pentathiepins can be equilibrated with trithioles and describe our results in this area as well as our initial forays into the chemical reactions of pentathiepins.

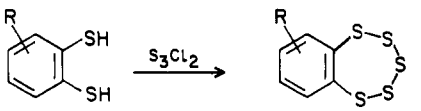
Synthesis

Our initial observation was that the disodium salt of 5-cyanoisothiazole-3,4-dithiol (**4**) reacted with excess sulfur monochloride to give **3**. Even when only 1 equiv of S_2Cl_2 was present, **3** was the only cyclic polysulfide detected. A considerable effort was made to prepare different sized polysulfides from **3**, without



4

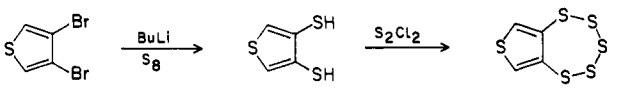
success. While **3** was an unusual compound, it was not the first pentathiepin to be prepared. Fehér and co-workers had successfully prepared benzopentathiepin **5a** and a few related compounds from benzene-1,2-dithiol and S_3Cl_2.[8] However, our result



5a R=H
b R=6-CH_3

suggests that dithiol-sulfur chloride intermediates can readily equilibrate and that the pentathiepin structure may be a thermodynamically favored product.

We turned our attention to appending the pentathiepin ring to other heterocycles. With the S_2Cl_2 procedure, the problem reduced to one of accessing the requisite vicinal dithiols. Gronowitz has described the preparation of thiophene-3,4-dithiol (**6**) from 3,4-dibromothiophene.[9] However, we found that his two-step



6 **7**

preparation, which required handling of the highly sensitive 4-bromothiophene-3-thiol, could be performed in one pot by simply employing 2 equiv of *n*-butyllithium and sulfur. **6** prepared in this manner could be purified by distillation; it was free of 3-thiophenethiol, but usually contained minor amounts of 4-butylthiophene-3-thiol. This impurity did not interfere with the subsequent cyclization. Slow addition of a dilute solution of **6** to a dilute solution of S_2Cl_2, both in degassed CH_2Cl_2, produces the new symmetrical pentathiepin **7**. Pure **7** can be isolated by molecular distillation, silica gel chromatography, and recrystallization from hexane in 2% overall yield from 3,4-dibromothiophene.

The synthesis of benzopentathiepins was now examined. Of the possible routes to the prerequisite vicinal dithiols,[10] we initially exploited the benzyne reaction with CS_2 and alcohols discovered by Nakayama.[11] The 2-alkoxybenzodithioles **8** obtained from

(1) Person to whom inquiries regarding the crystal structures should be sent.

(2) A complete listing is not feasible. Selected references are: Harpp, D. N.; Smith, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 6045-6053. Ballini, R. *Synthesis* **1982**, 834-836. Wratten, S. J.; Faulkner, D. J. *J. Org. Chem.* **1976**, *41*, 2465-2467. Chernyshev, E. A.; Kuz'min, O. V.; Lebedev, A. V.; Gusev, A. I.; Kirillova, N. I.; Nametkin, N. S.; Tyurin, V. D.; Krapivin, A. M.; Kubasova, N. A. *J. Organomet. Chem.* **1983**, *252*, 133-141. Anthoni, U.; Christophersen, C.; Jacobsen, N.; Svendsen, A. *Tetrahedron* **1982**, *38*, 2425-2427. Kato, A.; Hashimoto, Y.; Otsuka, I.; Nakatsu, K. *Chem. Lett.* **1978**, 1219-1222.

(3) Morita, K.; Kobayashi, S. *Chem. Pharm. Bull.* **1967**, *15*, 988-993; *Tetrahedron Lett.* **1966**, 573. Still, I. W. J.; Kutney, G. W. *Tetrahedron Lett.* **1981**, *22*, 1939-1940.

(4) Rahman, R.; Safe, S.; Taylor, J. *J. Chem. Soc. C* **1969**, 1665. Brewer, D.; Rahman, R.; Safe, S.; Taylor, A. *J. Chem. Soc., Chem. Commun.* **1968**, 1571.

(5) (a) Vladuchick, S. A.; Fukunaga, T.; Simmons, H. E.; Webster, O. W. *J. Org. Chem.* **1980**, *45*, 5122-5130. (b) Vladuchick, S. A. US Patent 4094985, June 13, 1978.

(6) Harpp, D. N.; Granata, A. *J. Org. Chem.* **1979**, *44*, 4144-4148.

(7) (a) Tebbe, F. N.; Wasserman, E.; Peet, W. G.; Vatvars, A. *J. Am. Chem. Soc.* **1982**, *104*, 4971-4972. (b) Steudel, R. *Curr. Top. Chem.* **1982**, *102*, 149-176 and references cited therein. (c) Steudel, R.; Steidel, J.; Pickardt, J.; Schuster, F. *Z. Naturforsch., B* **1980**, *35B*, 1378-1383.

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(9) Gronowitz, S.; Moses, P.; Hornfeldt, A. *Ark. Kemi* **1960**, *17*, 237. Gronowitz, S.; Moses, P. *Acta Chem. Scand.* **1962**, *16*, 105-110.

(10) (a) Benzene-1,2-dithiol and toluene-3,4-dithiol are available from Fluka. (b) Hünig, von S., Fleckenstein, E. *Liebigs Ann. Chem.* **1970**, *738*, 192-194.

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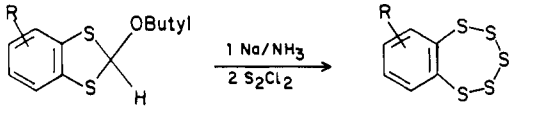
Table I. Crystallographic Information

	3	7	12d, R = Ph, R′ = H	5b	15, R = CF_3	
			(a) Crystal Data (Mo Kα radiation, λ = 0.71069 Å)			
formula	$C_4N_2S_6$	$C_4H_2S_6$	$C_9H_6N_2S_5$	$C_7H_6S_5$	$C_7H_2F_3NO_2S_3$	S_8
fw	268.44	242.44	258.41	250.45	285.29	256.51
cryst syst	monoclinic	orthorhombic	monoclinic	triclinic	monoclinic	orthorhombic
space group	$P2_1/c$	*Pbca*	$P2_1/c$	$p\bar{1}$	$P2_1/c$	*Fddd*
a, Å	16.722 (14)	7.811 (1)	14.852 (2)	7.829 (1)	15.376 (2)	10.389 (1)
b, Å	6.240 (5)	24.395 (2)	7.367 (1)	9.354 (1)	8.184 (2)	12.757 (1)
c, Å	9.249 (5)	8.867 (1)	12.305 (1)	7.760 (1)	7.816 (2)	24.426 (2)
α, deg				97.84 (1)		
β, deg	104.49 (5)		115.86 (1)	103.03 (1)	96.79 (1)	
γ, deg				112.23 (1)		
v, Å^3	934	1690	1212	497	977	3237
T, °C	26	−100	24	−100	−100	−100
Z	4	8	4	2	4	16
D_x, g cm^{-3}	1.908	1.906	1.417	1.674	1.940	2.105
μ, cm^{-1}	13.4	14.7	7.2	10.6	7.6	20.1
			(b) Data Collected on a Syntex P3 Diffractometer			
cryst dimen, mm	0.14 × 0.50 × 0.50	0.25 × 0.20 × 0.25	0.14 × 0.30 × 0.40	0.21 × 0.14 × 0.35	0.25 × 0.19 × 0.35	0.45 × 0.32 × 0.35
ω-scan range, deg	2.0	1.0	1.0	1.0	1.0	1.0
2θ range	4-55	4-52	4-55	4-55	4-50	4-55
reflect measd	2137	1656	2776	2281	1721	954
transmission factors	0.63-1.00	0.90-1.00	0.80-1.00	0.83-1.00	no change	no change
			(c) Full-Matrix Least-Squares Refinement			
anisotropic thermal parameters for	S, N, C	S, C	S, N, C	S, C	S, F, O, N, C	S
isotropic thermal parameters for		H	H	H	H	
variables	109	99	169	133	153	37
reflect used	1706	1382	2242	1877	1359	839
$F^2 > n\sigma(F^2)$, *n*	2.0	2.0	2.0	3.0	3.0	3.0
R	0.051	0.025	0.034	0.036	0.045	0.022
R_w	0.055	0.027	0.036	0.041	0.056	0.028
largest peak in final diff Fourier, eÅ^{-3}	0.57	0.30	0.23	1.26[a]	0.50	0.34

[a] One peak, located between C(1) and S(1), remains unexplained.

this reaction were conventionally reduced to benzene-1,2-dithiols with Na/NH_3.[12] For **8a** and **b**, the dithiols were obtained in high

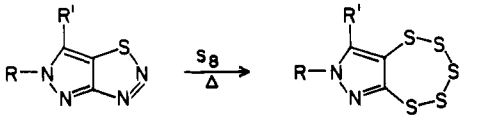


8a R=H
b R=4−CH_3
c R=5−Cl

5a R=H
b R=6−CH_3

yield and were isolated and characterized as their diacetates (**9a** and **b**). Not surprisingly **8c** suffered extensive dechlorination on treatment with Na/NH_3. Later, we found that **8a** and **c** could be conveniently hydrolyzed directly to the dithiols by treatment with mercuric acetate. The ortho dithiols could be reacted with S_2Cl_2 to give the corresponding benzopentathiepins **5**, using our standard conditions. We only prepared two benzopentathiepins **5a** and **b** by this procedure since we had simultaneously discovered a general route to **5** via the thermolysis of 1,2,3-benzothiadiazoles **10** with sulfur. The details of this reaction have been described elsewhere.[13]

We have subsequently found this thermolysis reaction to be broadly applicable to the synthesis of fused pentathiepins. For example, the pyrazolo-1,2,3-thiadiazoles **11**[13c] give moderate yields of pyrazolopentathiepins **12** when heated with sulfur at 130–180 °C. Interestingly, there is a 30–40 °C reduction in the reaction



11a R=CH_3 R′=H
b R=CH_3 R′=Br
c R=CH_3 R′=CO_2Et

12

temperature in going from the 6,5-fused 1,2,3-benzothiadiazoles to the 5,5-fused pyrazolo-1,2,3-thiadiazoles. This is presumably due to the greater inherent strain present in the latter.

The accessibility of a wide range of fused 1,2,3-thiadiazoles[14] makes this the method of choice for the synthesis of fused pentathiepins except in cases where vicinal dithiols are readily available.

Characterization

There are many problems inherent in the identification of polysulfides. These compounds (particularly linear polysulfides) are often formed as a mixture of isomers or equilibrate to mixtures on standing.[15] The use of reverse-phase HPLC has demonstrated

(11) Nakayama, J. *Synthesis* **1975**, 38–39.
(12) Degani has found that the fluoroborate salts of **8** can be reduced to ortho dithiols. We find that this step is not necessary. Degani, I.; Fochi, R. *Synthesis* **1976**, 471–472.
(13) (a) Chenard, B. L.; Miller, T. J. *J. Org. Chem.* **1984**, *49*, 1221–1224. (b) "Abstracts of Papers", 188th National Meeting of the American Chemical Society, Philadelphia, PA, Sept 1984; American Chemical Society: Washington, DC, 1984; ORGN 229. (c) Chenard, B. L. *J. Org. Chem.* **1984**, *49*, 1224–1227.
(14) For 1,2,3-benzothiadiazoles, see: Lionel, G. D. Ph.D. Dissertation, Cornell University, 1973. For other methods of 1,2,3-thiadiazole synthesis, see, for example: Shafiee, A. *J. Heterocycl. Chem.* **1978**, *15*, 473–475; *Ibid.* **1976**, *13*, 301–304. Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359–5364.
(15) Unpublished results from our lab (B. L. Chenard) with phenyl polysulfides.

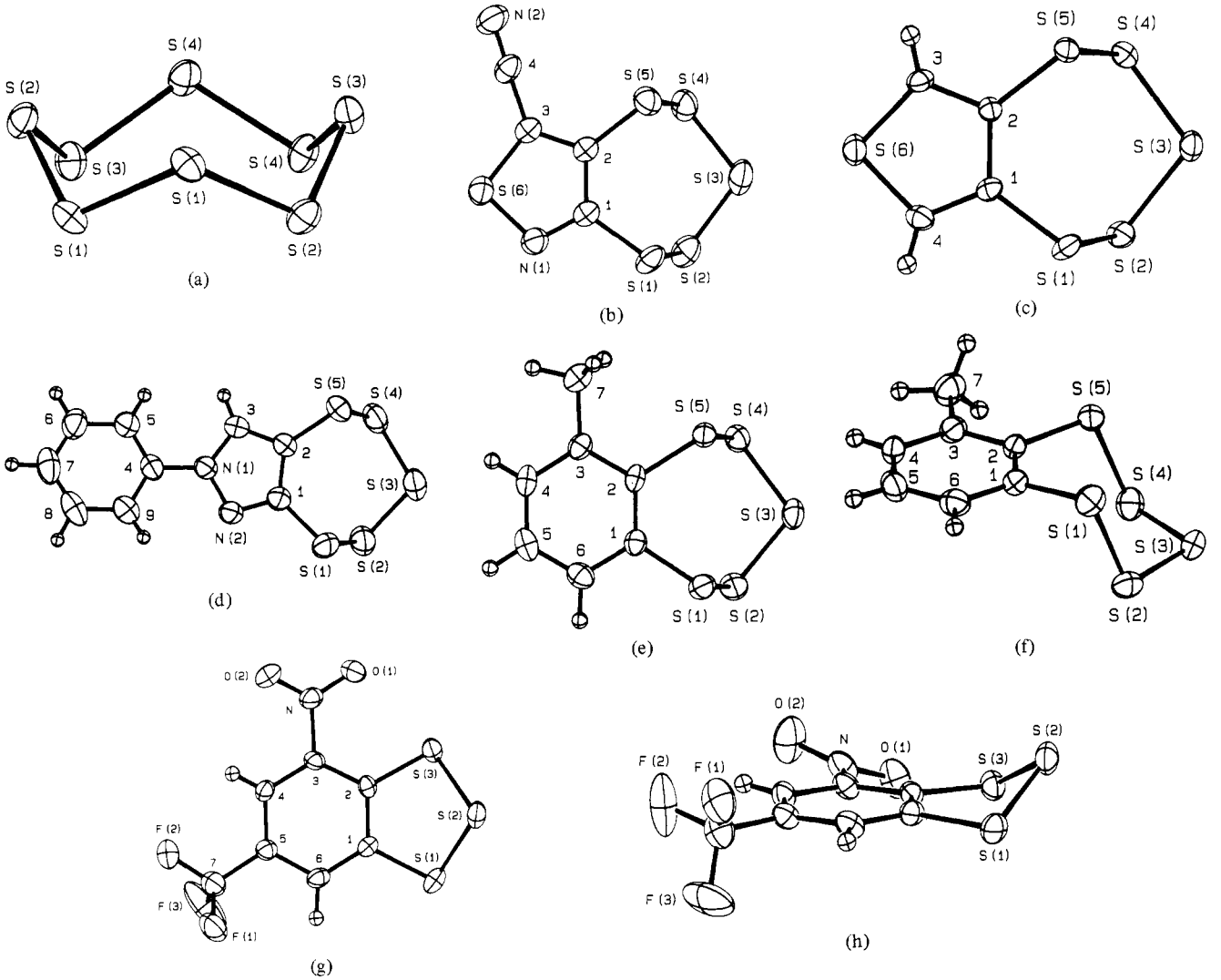


Figure 1. Molecular drawings of (a) S_8, (b) compound **3**, (c) compound **7**, (d) compound **12d**, R = Ph, R′ = H, (e) compound **5b**, view perpendicular to phenyl ring, (f) compound **5b**, side view showing the typical chair conformation of the C_2S_5 ring, (g) compound **15**, view perpendicular to phenyl ring, (h) compound **15**, side view showing the envelope conformation of the C_2S_3 ring.

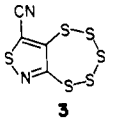
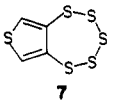
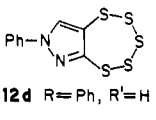
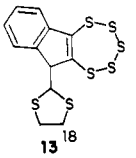
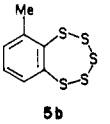
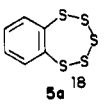
that many reactions previously described as yielding homogeneous products in fact give gross mixtures.[16] In his work on the synthesis of cyclic trisulfides, Harpp found that cryoscopic molecular weight determination was the only means to ensure chemical integrity.[6] Mass spectrometry may also be a misleading method for analysis as dimers and larger polysulfide decomposition products are often thermolyzed on the probe to give false monomeric parent peaks.[6,17] Therefore, to verify the structure of our pentathiepins, several of them were subjected to X-ray analysis.

The crystallographic information is described in Table I, with further details in the supplementary material. Drawings of the compounds are shown in Figure 1. The geometric parameters are presented in Table II along with the results of two previously reported pentathiepin X-ray analyses.[18] A redetermination of the orthorhombic form of S_8 has also been completed as a calibration for the other structure determinations; the average geometry (S–S, 2.051 Å; S–S–S, 108.14°; S–S–S–S, 98.04°) is in excellent agreement with that obtained in a low-temperature study by Coppens and co-workers.[19]

The similarity of the S–S bond lengths within this group of C_2S_5 pentathiepins is quite remarkable considering that related structures show wide variation in S–S distances. Related structures include seven-membered rings with sulfur substituted for carbon to form CS_6 and S_7 rings, and six-membered pentasulfide rings containing a carbon atom (CS_5) or a metal atom (MS_5) as the sixth member. Alternating long–short bonds, usually ranging from 2.02 to 2.08 Å, have been reported in hexathiepane (CH_2S_6), pentathiane (CH_2S_5), and dibenzylpentathiane [$(PhCH_2)_2CS_5$].[20] Of all the related structures, S_7 shows the most variation in S–S bond lengths: 1.995–2.182 Å.[7c] Among the organometallic complexes with MS_5 rings, the amount of variation is highly dependent on the nature of the metal atom.[21] The consistency of the S–S bond lengths within each pentathiepin presented here is thus quite unusual and most closely parallels the structural results for S_6[22] and S_8. The average bond length for the six pentathiepins is 2.052 Å, for S_6, 2.057 Å, and for S_8, 2.051 Å. The S–S–S bond angles and S–S–S–S torsional angles of the pentathiepins are between the average S_6 and S_8 values: 102.2° and 74.5° for S_6 and 108.1° and 98.0° for S_8. From these observations, we conclude that the stability and reactivity of the pentathiepins should approach that for S_8.

(16) Berany, G.; Mott, A. W. *J. Org. Chem.* **1984**, *49*, 1043–1051.
(17) See later in this text. We also suspect this to be likely for Fehér's tentatively identified benzotrithioles (see ref 8b) and: Fehér, F.; Glinka, K.; Malcharek, F. *Angew Chem., Int. Ed. Engl.* **1971**, *10*, 413–414.
(18) For **13**: Korp, J. D.; Bernal, I.; Watkins, S. F.; Fronczek, F. R. *J. Heterocycl. Chem.* **1982**, *19*, 459–462. For **5a**: Fehér, F.; Engelen, B. *Z. Anorg. Allg. Chem.* **1979**, *452*, 37–42.
(19) Coppens, P.; Yang, Y. W.; Blessing, R. H.; Cooper, W. F.; Larsen, F. K. *J. Am. Chem. Soc.* **1977**, *99*, 760–766.
(20) Fehér, F.; Lex, J. *Z. Anorg. Allg. Chem.* **1976**, *423*, 103–111.
(21) (a) Burshka, C.; Leonard, K.; Werner, H. *Z. Anorg. Allg. Chem.* **1980**, *464*, 30–36. (b) Muller, E. G.; Petersen, J. L.; Dahl, L. F. *J. Organomet. Chem.* **1976**, *111*, 91–112 and references cited therein.
(22) Donohue, J.; Caron, A.; Goldish, E. *J. Am. Chem. Soc.* **1961**, *83*, 3748.

Table II. Pentathiepin Geometry

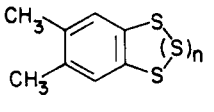
	 3	 7	 12d R=Ph, R'=H	 13[18]	 5b	 5a[18]
			Bond Lengths, Å			
C(1)–C(2)	1.421 (3)	1.440 (3)	1.415 (2)	1.355 (4)	1.398 (2)	1.382 (8)
C(1)–S(1)	1.774 (2)	1.761 (2)	1.755 (1)	1.767 (3)	1.773 (2)	1.774 (5)
C(2)–S(5)	1.765 (2)	1.758 (2)	1.744 (1)	1.756 (3)	1.795 (2)	1.777 (5)
S(1)–S(2)	2.051 (1)	2.052 (1)	2.043 (1)	2.051 (1)	2.047 (1)	2.041 (2)
S(4)–S(5)	2.055 (1)	2.055 (1)	2.053 (1)	2.055 (1)	2.055 (1)	2.048 (2)
S(2)–S(3)	2.063 (1)	2.056 (1)	2.051 (1)	2.052 (2)	2.055 (1)	2.045 (2)
S(3)–S(4)	2.053 (1)	2.057 (1)	0.054 (1)	2.050 (1)	2.058 (1)	2.039 (2)
S(1)—S(5)	3.518 (1)	3.531 (1)	3.612 (1)	3.461 (2)	3.308 (1)	3.366 (3)
S(2)—S(4)	3.247 (1)	3.223 (1)	3.232 (1)	3.205 (2)	3.227 (1)	3.192 (3)
			Bond Angles, deg			
C(2)–C(1)–S(1)	125.9 (2)	126.3 (2)	128.4 (1)	124.7 (2)	123.3 (1)	123.7 (4)
C(1)–C(2)–S(5)	126.7 (2)	126.6 (2)	129.3 (1)	128.8 (2)	121.4 (1)	124.2 (4)
C(1)–S(1)–S(2)	102.48 (8)	104.58 (7)	103.41 (5)	104.5 (1)	103.02 (6)	104.5 (2)
C(2)–S(5)–S(4)	102.70 (8)	105.89 (7)	103.33 (5)	104.7 (1)	104.22 (6)	104.6 (2)
S(1)–S(2)–S(3)	104.47 (4)	104.57 (3)	105.53 (3)	104.4 (1)	103.80 (3)	104.6 (1)
S(3)–S(4)–S(5)	104.78 (4)	104.56 (3)	105.06 (3)	104.4 (1)	104.55 (3)	105.1 (1)
S(2)–S(3)–S(4)	104.16 (4)	103.17 (3)	103.89 (3)	102.8 (1)	103.38 (3)	102.8 (1)
			Torsional Angles, deg			
S(1)–C(1)–C(2)–S(5)	−1.5	−3.1	−1.9	−1.2	1.7	0.4
C(1)–S(1)–S(2)–S(3)	88.9	89.4	85.6	89.4	93.5	88.6
C(2)–S(5)–S(4)–S(3)	−87.8	−86.5	−85.1	−86.9	−91.8	−89.5
S(1)–S(2)–S(3)–S(4)	−77.5	−79.6	−79.2	−77.9	−73.7	−74.8
S(5)–S(4)–S(3)–S(2)	76.6	76.9	78.5	76.8	72.9	74.7

We have further characterized the pentathiepins by their laser Raman spectra (Figure 2). Throughout the series there is a strong absorption in the 485-cm^{-1} region. This is often a two-bond absorption with the higher one (490 ± 5 cm^{-1}) always being the stronger. Beyond this region, one must examine the individual subgroups for similarities. We have examined too few pyrazolo- and thienopentathiepins to identify any band patterns; however, the benzopentathiepins have two additional characteristic adsorptions, a weak-to-moderate absorption at 425 ± 5 cm^{-1} and a strong band at 180 ± 5 cm^{-1}. These additional bands may be very useful for the identification of benzopentathiepins.

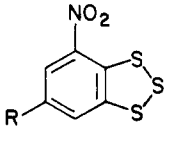
The UV spectra of the pentathiepins (Table III) were also recorded. In later work on the equilibration of these molecules, the UV spectra proved to be invaluable. For the benzopentathiepins, there was only one λ_{max} at 208 ± 5 nm (ϵ = 30000). This was in good agreement with that reported for **5a**.[8a] Shoulders which tail off into the visible region account for the pentathiepins' pale-yellow appearance. The λ_{max} for the pyrazolopentathiepins was shifted to 225 nm, but since methylene chloride was the solvent, it is likely that other maxima may also be present below 220 nm.

Equilibration Studies

Our interest in exploring the equilibration of pentathiepins stems from the observations of Fehér and co-workers that the various benzopolysulfides **14** (n = 2, 3, and 5) could be prepared from the corresponding dithiol and the proper poly(sulfanyl chloride).[8b]



14



15

Fehér also noted that **14** (n = 1) was prepared as an unstable oil. Additionally, Rasheed has prepared several benzotrithioles **15** which all contain a nitro group at C-4.[23] As Rasheed's **15** were the only benzotrithioles reported to be stable, we prepared **15** (R = CF_3) and obtained an X-ray analysis to verify its structure[24] (Figure 1). The results have been compared with **16** (Table IV), the only trithiole with a recorded X-ray analysis.[25] While **16** has

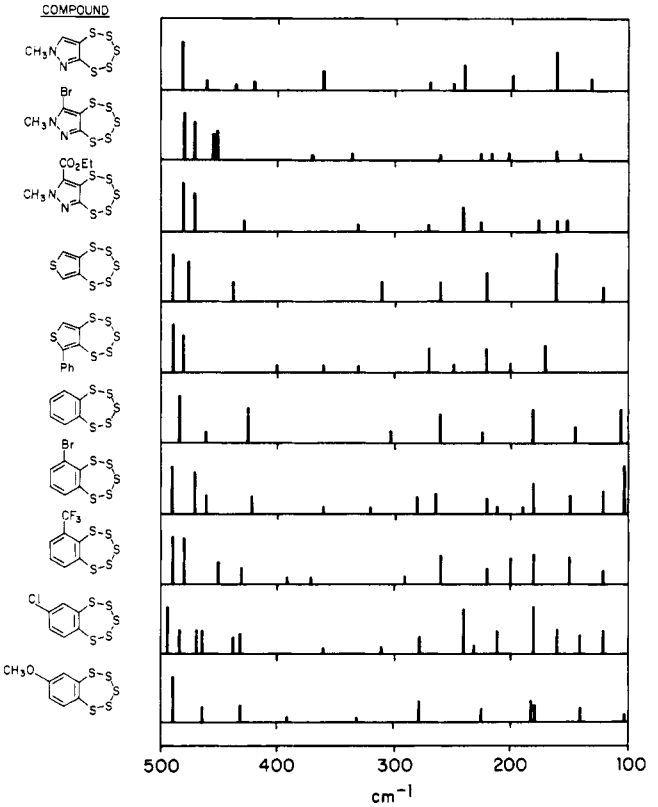


Figure 2. Schematic representation of the Raman spectra of pentathiepins from 500 to 100 cm^{-1}.

(23) Rasheed, K.; Warkentin, J. D. *J. Org. Chem.* **1980**, *45*, 4806–4807.

(24) We thank Dr. W. K. Moberg for preparing this compound.

(25) Emsley, J.; Griffiths, D. W.; Osborn, R. *J. Chem. Soc., Chem. Commun.* **1978**, 658; *Acta Crystallogr., Sect. B* **1979**, *B35*, 2119–2121.

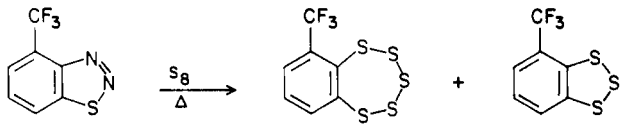
Table III. UV Spectra of Selected Polysulfides

compound	solvent	λ (ε)				
		Pentathiepins				
5a, R = H	hexane	211 (30 950)	270 (sh)		325 (sh)	
5c, R = 6-CF_3	hexane	212 (32 500)	262 (sh)		340 (sh)	
5d, R = 7-CF_3	hexane	208 (37 400)	275 (sh)		330 (sh)	
5e, R = 6-Br	hexane	204 (29 500)	235 (sh)	305 (sh)	345 (sh)	
5g, R = 6-$CH_2CO_2CH_3$	hexane	212 (26 300)	230 (sh)		329 (sh)	
12, R = CH_3, R′ = H	CH_2Cl_2	223 (13 200)	275 (sh)			
12b, R = CH_3, R′ = Br	CH_2Cl_2	230 (17 100)	275 (sh)			
		Benzotrithioles[a]				
17c, R = 4-CF_3	hexane	205 (22 250)	238 (3300)		286 (3090)	323 (sh)
17e, R = 4-Br	hexane	206 (15 550)	238 (3750)	253 (sh)	278 (3250)	321 (sh)
17g, R = 4-$CH_2CO_2CH_3$	10% H_2O–CH_3OH[b]	212	241 (sh)		267	307 370
17i, R = 4,6-$C(CH_3)_3$	CH_3OH[b]	205	225 (sh)	245 (sh)	275	320 (sh)

[a] ε determined by concentration of an aliquot of the sample. [b] Solution too dilute to accurately measure weight for calculation of ε.

a saturated C–C bond in the trithiole ring which perturbs some of the bond angles and lengths, overall there is good agreement for the sulfur parameters.

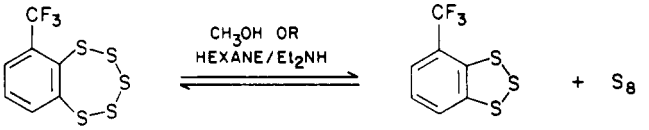
We wanted to probe the steric and electronic factors which influence the polysulfide ring size so that we could tailor future syntheses according to these factors. Our first hint that equilibration might be possible came from the preparation of 6-(trifluoromethyl)benzopentathiepin (**5c**) by thermolysis of **10c** (R = 4-CF_3). Along with **5c**, another compound was obtained in low yield (2–5%). This compound was easily isolated by HPLC (see



10c **5c** **17c**

Experimental Section); however, when the dilute hexane solutions were concentrated, the compound polymerized. The mass spectrum of this polymeric material shows a base peak at *m/e* 240 (which we attribute to depolymerization) along with many higher molecular weight peaks. If the hexane solution of this unknown compound is analyzed by GC/MS, the parent ion (and base peak) is *m/e* 240. There are no higher molecular weight fragments out to *m/e* 650. This is consistent with the formation of **17c**. The UV spectrum of **17c** (Table III) was distinctly different from that of **5c**, and in subsequent experiments, these spectra along with GC/MS and HPLC retentions provided the basis for identification of the benzotrithioles.

Examination of **5c** by reverse-phase HPLC revealed that the compound readily equilibrated to a mixture of **5c**, **17c**, and S_8 in methanol. The reaction was very clean as only the three



5c **17c**

components were observed by HPLC and only **5c** and **17c** were seen by 400-MHz ^{19}F NMR. The initial rate for the equilibration (2.1×10^{-4} s^{-1} at 22.5 °C) was determined by both ^{19}F NMR and HPLC with the equilibrium being reached with a **5c**/**17c** ratio of 46:54. The reaction was first order in **5c** as the rate was identical at half the **5c** concentration. We also observed no deuterium isotope effect on changing from CH_3OH to CD_3OD as solvent, indicating that proton transfer was not important at the rate-determining step. This equilibration is reminiscent of the one recently reported for S_8 and its allotropes S_6 and S_7.[7a] No reaction takes place in hexane; however, if diethylamine is added, the same equilibrium is obtained. Hexane solutions of **17c** spiked with S_8 alone were reluctant to regenerate the equilibrium; however, if diethylamine (0.5–2 equiv) was added, the reverse equilibration was set up. The above observations are consistent with a base-catalyzed equilibrium of **5c** with **17c** and S_8.

The corresponding 7-(trifluoromethyl)benzopentathiepin **5d** in dilute methanol solution was subsequently found to be stable for at least 7 days at ambient temperature as judged by HPLC. We surmised that the equilibration was a purely steric consequence and continued exploring the equilibria with 6-substituted benzopentathiepins. The 6-bromobenzopentathiepin **5e** will also generate some benzotrithiole **17e** when dissolved in methanol. Again **17e** was identified by GC/MS and UV (Table III). This time, however, the reaction was not a simple equilibrium. Instead several new unidentified components were also observed. The amount of **17e** which formed in the reaction seemed to reach a steady-state concentration estimated to be ca. 5% while the pentathiepin was gradually decomposed. Solutions of **17e** in hexane seemed to be reasonably stable when stored in brown bottles. These solutions when treated with S_8 and Et_2NH quickly regenerated **5e** along with another product presumed to be a dimer of the same type as that reported earlier by Fehér.[8b] This dimeric compound did not produce a parent ion in the mass spectrum.

We were very surprised when we attempted to equilibrate **5b**. On the basis of the above observations, **5b** should produce a significant amount of **17b** since sterically a CH_3 is between Br and CF_3.[26] In the event, no **17b** was observed when **5b** was dissolved in methanol. Equally surprising, **5f** [R = 6,7-$(Me_2N)_2$] also showed no propensity to equilibrate in methanol.[27] These results suggest that an ortho electron-withdrawing substituent may be much more important than mere steric bulk in order to stabilize benzotrithioles. This is consistent with Rasheed's observations.[23]

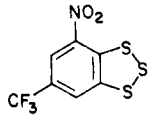
To further test the steric requirements of benzopolysulfides, the 1,2,3-benzothiadiazoles **10g–i** were prepared[28] and thermolyzed with sulfur. (The ester in **10g** and **h** should exert very little electron-withdrawing effect since it is separated from the benzene ring by a carbon atom.) The polysulfides obtained from this reaction are summarized in Table V. Thus, **10g** was converted solely to **5g**.[27] When **10h** was thermolyzed, a ca. 1:1 mixture of **5h** and **17h** was obtained. These compounds were extremely difficult to separate even by HPLC. While we were able to obtain samples enriched in **5h** and **17h** which were suitable for GC/MS analysis, the samples contained enough overlap so that the UV spectrum of **5h** overpowered that of **17h**. When **10i** was thermolyzed, a 9:91 mixture of **5i**/**17i** was produced. Thus, we were

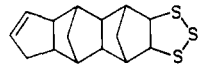
(26) Estimation based on *A* strain values for Br (0.38) and CH_3 (1.70). We would expect the CF_3 value to be somewhat larger than that for CH_3.

(27) **5b**, **f**, and **g** could be forced to produce small amounts of **17b**, **f** and **g** by decomposing them in a large excess of diethylamine.

(28) Details of these syntheses will be published elsewhere.

Table IV. Trithiole Geometry





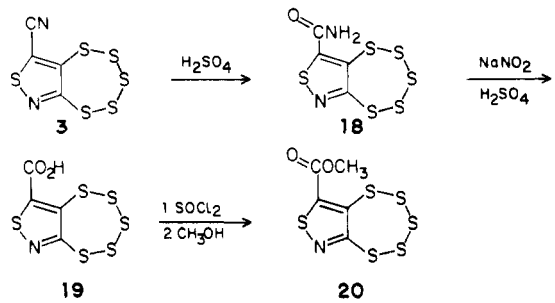
	15 R=CF_3	**16**[25]
	Bond Lengths, Å	
C(1)–C(2)	1.406 (4)	1.572 (4)
C(1)–S(1)	1.777 (3)	1.833 (3)
C(2)–S(3)	1.762 (2)	1.839 (4)
S(1)–S(2)	2.065 (1)	2.046 (1)
S(2)–S(3)	2.071 (1)	2.047 (2)
S(1)—S(3)	3.056 (1)	2.978 (2)
	Bond Angles, deg	
C(2)–C(1)–S(1)	117.5 (2)	112.6 (3)
C(1)–C(2)–S(3)	118.1 (2)	112.4 (3)
C(1)–S(1)–S(2)	94.1 (1)	94.2 (1)
C(2)–S(3)–S(2)	94.3 (1)	94.3 (1)
S(1)–S(2)–S(3)	95.27 (4)	93.4 (1)
	Torsional Angles, deg	
S(1)–C(1)–C(2)–S(3)	−0.6	−0.8
C(2)–C(1)–S(1)–S(2)	29.3	35.5
C(1)–C(2)–S(3)–S(2)	−28.4	−34.2
C(2)–S(3)–S(2)–S(1)	39.2	50.2
C(1)–S(1)–S(2)–S(3)	−39.3	−50.6

finally able to prepare a system with an ortho electron-donating group in which the benzotrithiole was the predominant product.

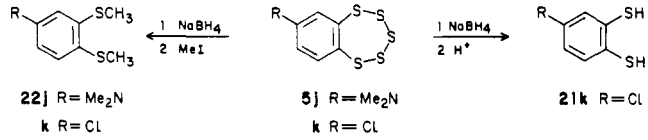
In this study, we have explored a region of borderline stability with regard to substituted benzotrithioles and benzopentathiepins. We conclude that their stability is based on a combination of both steric and electronic effects. Benzotrithioles will only be preferred when there is an electron-withdrawing group ortho to the polysulfide ring or when a very bulky ortho electron-donating group is present. In all other cases, the benzopentathiepin will be the preferred polysulfide. Noticeably absent from this discussion is any reference to the benzotetrathiin (i.e., **14**, $n = 2$). We have been unable to identify any species corresponding to a tetrathiin during the course of these experiments. It would seem reasonable that a benzotetrathiin should have an HPLC retention time intermediate between a benzotrithiole and a pentathiepin. In only one case, the equilibration of **5h** with methanol–Et_2NH, did we see evidence for such a species. During this equilibration, a transient peak was observed between peaks for **5h** and **17h**. We were unable to demonstrate conclusively whether or not this peak was a benzotetrathiin. The fact that we don't see a tetrathiin raises the question of the nature of the departing sulfur fragment during the equilibration of **5** with **17**. It is intriguing to speculate on the possibility that an "S_2" fragment is eliminated although we have not addressed this question as yet.[29]

Reactions of Pentathiepins

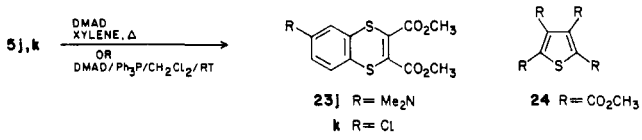
We separate this section into (1) reactions performed on the fused ring or its substituents which leave the pentathiepin ring intact and (2) reactions performed on the pentathiepin ring which lead to new compounds no longer containing the pentathiepin unit. We find that the pentathiepin ring has considerable stability toward acidic reagents which allows substituent manipulation. For example, the cyano group in **3** can be readily hydrolyzed to the corresponding amide **18** (94%) in cold sulfuric acid. The amide can be further hydrolyzed to the acid **19** (51%) on treatment with $NaNO_2$ in H_2SO_4. When standard conditions were used, **19** was converted to its acid chloride which was subsequently reacted with alcohols or amines to give esters or amides, respectively. This process is illustrated here with the simple case of **20**. A few attempts at electrophilic aromatic substitution were attempted with **5j** ($POCl_3$–DMF, Cl_2CHOCH_3–$SnCl_4$); however, only starting material (30–80%) was recovered in all cases.



We have only begun to explore the reactions of the pentathiepin ring and report on two of them. Sodium borohydride cleanly reduces benzopentathiepins **5j** and **k** to dithiols. After acidification, the known **21k**[30] was obtained in 49% distilled yield as a white solid. Alternatively, methylation of the crude reaction mixture gave **22j** and **k** (81% and 67%, respectively).



Dimethyl acetylenedicarboxylate, DMAD, slowly reacts with pentathiepins **5j** and **k** in refluxing xylene to give 1,4-benzodithiins **23j** and **k** in low yield (30% and 15%, respectively). It was difficult to force these reactions to completion. Long reaction time and excess DMAD only increased the amount of tetracarbomethoxythiophene (**24**) and benzothiophene side products. However, the reaction can be performed at room temperature by dropwise addition of triphenylphosphine to a CH_2Cl_2 solution of **5j** and DMAD to give **23j** in 51% yield.[31] It should be noted that Nakayama has prepared some of these compounds by an unrelated route,[32] and Rauchfuss has demonstrated the analogous chemistry with Cp_2TiS_5 and DMAD.[33]



Conclusion

In summary, we have examined a variety of methods to prepare fused pentathiepins. Of these, the most generally applicable is the thermolysis of fused thiadiazoles with sulfur. Where vicinal dithiols are readily available, their reaction with S_2Cl_2 is the method of choice to prepare the polysulfides. The X-ray analysis of several representative pentathiepins rigorously established their identity.

We have observed for the first time the equilibration of a pentathiepin (**5c**) with a trithiole (**17c**) and have found that in general pentathiepins with "ortho" substituents can be forced to disproportionate to produce trithioles. We have been unable to

(29) The capture of "S_2" in solution has been recently reported. Steliou, K.; Gareau, Y.; Harpp, D. N. *J. Am. Chem. Soc.* **1984**, *106*, 799–801.

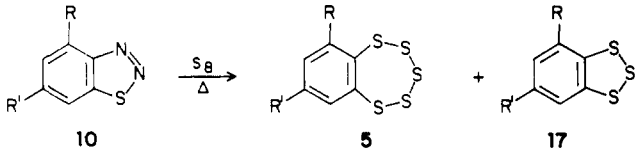
(30) Mills, W. H.; Clark, R. E. D. *J. Chem. Soc.* **1936**, 175–181.

(31) We thank Dr. Fred N. Tebbe for this suggestion.

(32) Nakayama, J.; Fukushima, H.; Hashimoto, R.; Hoshino, M. *J. Chem. Soc., Chem. Commun.* **1982**, 612–613.

(33) Bolinger, C. M.; Rauchfuss, T. B. *Inorg. Chem.* **1982**, *21*, 3947–3954.

Table V. Thermolysis of **10** with Sulfur



10 **5** **17**

compd	R	R′	5/17	tot % yield
10g	$CH_2CO_2CH_3$	H	100:0	55
10h	$CH(CH_3)CO_2CH_3$	H	~50:50	57
10i	$C(CH_3)_3$	$C(CH_3)_3$	9:91	25

establish the intermediacy of tetrathiins in these reactions. The trithioles are relatively unstable molecules; however, they show increasing stability with strong ortho electron-withdrawing substituents or when there is sufficient steric bulk to protect them from undergoing further transformations. The identity of our relatively unstable trithioles rests on their GC/MS and UV spectroscopic data, and the identity of the one known trithiole (**15**) was firmly established by X-ray analysis.

Finally, we have begun an examination of the chemical reactivity of the pentathiepin ring. From these early results, we conclude that reactions requiring acidic media may be performed in the presence of a pentathiepin, while, not surprisingly, basic reaction conditions cause ring cleavage to occur often with the formation of novel ring systems. There is certainly much more interesting chemistry of cyclic polysulfides to be explored in this area.

Experimental Section

General Procedures. Melting points were taken with a Thomas Hoover or a Buchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 7199 FT infrared spectrometer and are reported in reciprocal centimeters unless otherwise stated. Only strong bands are reported unless otherwise stated. Routine proton NMR spectra were obtained at either 80 or 90 MHz with a Varian EM390 or an IBM NR80 FT instrument. NMR data are reported in parts per million (δ) downfield from tetramethylsilane in deuteriochloroform. Analyses were determined by either MicroAnalysis Inc., Wilmington, DE, or our own analysis group.

8-Cyanoisothiazolopentathiepin (3). The synthesis has been described elsewhere.[5]

Thiophene-3,4-dithiol (6). A solution of 3,4-dibromothiophene (Fairfield Chemical Co., 10.0 g, 41.3 mmol) in ether (25 mL) was added at −70 °C to 1.6 M *n*-butyllithium in hexane (52 mL, 83.0 mmol) under nitrogen, and the mixture was stirred for 5–10 min at −70 °C. The mixture was treated with flowers of sulfur (2.66 g, 83.0 mmol) and stirred at −70 °C for 30 min. The mixture was poured into 100 mL of water and separated, and the ether layer was extracted with 3 × 25 mL of 2 N NaOH and discarded. The combined aqueous layers were cooled with ice and acidified with 10% sulfuric acid to liberate the dithiol from its sodium salt. The product was extracted with 3 × 50 mL of ether, and the extracts were dried over sodium sulfate and evaporated to leave ~6.5 g of crude product which was fractionated in a micro-Vigreaux apparatus. The material with bp 23–30 °C/0.1 mmHg (0.57 g) was thiophene-3-thiol, that with bp 59–65 °C/0.1 mmHg (2.47 g) was a 16:62:22 mixture of thiophene-3 thiol/thiophene-3,4-dithiol/4-butylthiophene-3-thiol, and that with bp 65–75 °C/0.1 mmHg was an 87:13 mixture of thiophene-3,4 dithiol/4-butylthiophene-3-thiol (0.93 g). The identities and ratios of these components were estimated by integration of their 90-MHz NMR spectra, compared with authentic samples.[9] Thiophene-3-thiol has signals at δ 7.17 (m, 1 H), 7.03 (m, 1 H), 6.86 (m, 1 H), and 3.33 (s, 1 H), thiophene-3,4-dithiol has signals at δ 7.19 (s, 2 H) and 3.44 (s, 1 H), and 4-butylthiophene-3-thiol has signals at δ 7.19 (m, 2 H), 2.97–2.59 (m, 2 H), 1.83–1.14 (m, 4 H), and 0.89 (t, J = 7 Hz, 3 H). The positions of the SH signals of the mono- and dithiol were remarkably constant from run to run. The thiophenethiols have noxious odors; glassware is conveniently decontaminated with Chlorox.

Thieno[3,4-*f*]-1,2,3,4,5-pentathiepin (7). Thiophene-3,4-dithiol, prepared as above (14.62 g, 99.0 mmol), was dissolved in dichloromethane (100 mL), which had been degassed by boiling and allowed to cool with nitrogen sparging, and was added slowly to a stirred solution of sulfur monochloride (27.0 g, 200 mmol) in similar dichloromethane (500 mL). In these reactions, we found it advantageous not only to degas and sparge the solvent with nitrogen but also to maintain an active stream of nitrogen through the liquid during the reaction. After the addition was complete, the mixture was stirred at 25 °C for 2 h, swept with nitrogen for 30 min to remove volatile materials, and then washed with 250-mL portions of 5% sodium bicarbonate and 10% NaOH to remove HCl and unreacted thiols. The dichloromethane layer was dried over sodium sulfate and evaporated to leave a yellow residue which was separated into two fractions by Kugelrohr distillation: (1) 3.05 g, 140–155 °C/0.4 mmHg pot temperature and (2) 6.66 g, 155–170 °C/0.4 mmHg pot temperature. The 3.05-g fraction was discarded, and the 6.66-g fraction, which was shown to contain pentathiepin by mass spectrum, was dissolved in dichloromethane, filtered free of insoluble materials (0.23 g), and separated by HPLC on silica columns (Waters Assoc.), using hexane as the eluent. Three fractions were separated and identified by their spectra: (1) sulfur (1.07 g), discarded; (2) pentathiepin (1.07 g); and (3) a mixture of unidentified materials (1.85 g). Fraction 2 was recrystallized from hexane by first dissolving it in dichloromethane (50 mL), treating with Darco, and then diluting the filtrate with 50 mL of hexane to cloud point and seeding with crystals obtained from trial experiments. Recovery was 1.03 g (4.25 mmol, 2% overall from 3,4-dibromothiophene) of long yellow needles, mp 83–84 °C. Pure thieno[3,4-*f*]-1,2,3,4,5-pentathiepin, after drying at 25 °C/0.1 mmHg has IR ν_{max}(KBr) 3090, 1527, 1465, 850, and 800 cm^{-1}; Raman spectrum, ν_{max} 1395, 1370, 1115, 490, 470, and 435 cm^{-1}; UV λ_{max} (EtOH) 235 nm (ϵ 16 820) and 270 (5990); NMR δ 7.52 (s, 2 H). Anal. Calcd for $C_4H_2S_6$: C, 19.82; H, 0.83; S, 79.35. Found: C, 20.17; H, 0.95; S, 79.51.

7-Methylpyrazolopentathiepin (12a). A mixture of sulfur (0.91 g, 3.57 mmol), 5-(methylpyrazolo)-1,2,3-thiadiazole (**11a**, 0.5 g, 3.57 mmol), and decalin (5 mL) was heated to 130 °C for 1 h. Nitrogen evolved steadily during this time. The mixture was cooled, and the solvent was removed by Kugelrohr distillation at 50 °C (0.5 mmHz). The residue was chromatographed on Silica Woelm TSC (100 g) with a methylene chloride–hexane gradient to give first sulfur and then 0.31 g, 36%, of 7-methylpyrazolopentathiepin (**12a**) as an off-white solid. A sample recrystallized from ethyl acetate–hexane had mp 114–116 °C: IR (KBr) 3110, 3085, 1490, 1340, 1135, 1000, 715, 688 cm^{-1}; mass spectrum (low resolution), m/e 240 which were identical with that of an authentic sample.[34]

8-Bromo-7-methylpyrazolopentathiepin (12b) was prepared as for **12a** from sulfur (0.58 g, 2.28 mmol), 6-bromo-5-methylpyrazolo-1,2,3-thiadiazole (**11b**, 0.5 g, 2.28 mmol), and decalin (5 mL at 130 °C for 1.5 h to yield 0.32 g (44%) as a sticky solid). A sample recrystallized from ether–hexane had mp 139–141 °C: ^{1}H NMR δ 3.89 (s, 3 H); IR (KBr) 1451, 1332 cm^{-1}.

Anal. Calcd for $C_4H_3BrNS_5$: C, 15.05; H, 0.95; S, 50.21. Found: C, 14.81; H, 1.06; S, 50.37.

8-Carboethoxy-7-methylpyrazolopentathiepin (12c) was prepared as for **12a** from sulfur (0.51 g, 2.03 mmol), 6-carboethoxy-5-methylpyrazolo-1,2,3-thiadiazole (**11c**, 0.43 g, 2.03 mmol), and decalin (5 mL) at 170 °C for 1 h to yield 0.24 g, 38%, of **12c** as an oil: ^{1}H NMR δ 4.45 (q, 2 H), 4.15 (s, 3 H), 1.41 (t, 3 H); IR (neat) 1720, 1251, 1110 cm^{-1}; mass spectrum, m/e 311.9198, m/e calcd for $C_7H_8N_2O_2S_5$ 311.9189.

6-Methylbenzopentathiepin (5b). Ammonia (75 mL) was condensed into a solution of 4-methyl-2-butoxy-1,3-benzodithiole (**8b**) (5.37 g, 22.3 mmol) and THF (75 mL). Sodium (2.57 g, 111.8 mmol) was added as small chips over 5 min, and the solution turned deep blue. The mixture was allowed to reflux 30 min, and then solid ammonium chloride (5.98 g, 111.8 mmol) was added in small portions. The ammonia was evaporated with the aid of a water bath and nitrogen purge. The residual white slurry was diluted with THF (100 mL) and cooled to 0 °C. Sulfur monochloride (3.57 mL, 44.6 mmol) dissolved in THF (30 mL) was added dropwise over 35 min followed by stirring overnight at ambient temperature. The THF was removed at reduced pressure, and methylene chloride (150 mL) was added. Insoluble sulfur was filtered through Celite, and the filtrate was extracted with 5% sodium bicarbonate, water, and brine and then dried through a cone of sodium sulfate. Concentration left 5 g of an orange oil which was chromatographed on silica (250 g). Elution with 2% methylene chloride/hexane proceeded as follows: 400 mL, nil; 200 mL, unweighed, sulfur; 100 mL, 0.56 g of sulfur-product mixture; 300 mL, 2.17 g, 38%, of 6-methylbenzopentathiepin as a yellow oil. Further purification by HPLC (Zorbax Silica, hexane) gave an off-white solid which was recrystallized from hexane: mp 51–53 °C; NMR (360 MHz) δ 7.7 (dd, J = 1.2, 7.6 Hz, 1 H), 7.3 (partially obscured dd under $CHCl_3$, 1 H), 7.2 (t, J = 7.6 Hz, 1 H), 2.63 (s, 3 H); IR (KBr) 1440 (m), 1372 (m), 780, 711 (m) cm^{-1}.

Anal. Calcd for $C_7H_6S_5$: C, 33.57; H, 2.42. Found: C, 33.52; H, 2.33.

The preparation of benzopentathiepins **5c–e** has been previously described.[13a]

6,7-Bis(dimethylamino)benzopentathiepin (5f). A mixture of sulfur (2.3 g, 9 mmol), 4,5-bis(dimethylamino)-1,2,3-benzothiadiazole (2.0 g,

(34) Moberg, W. K. US Patent 4 275 073, 1981.

9 mmol), and decalin (30 mL) was heated to 175 °C for 1.4 h while nitrogen gas steadily evolved. The orange solution was cooled, and the decalin was removed by Kugelrohr distillation at 50 °C (0.5 mmHg). The residue was flash-chromatographed on silica (2 × 6 in., 1% ether-hexane) to give first sulfur and then 2.04 g (70%) of **5f** as an orange oil which solidified when scratched (mp 57–61 °C). A sample recrystallized from hexane at −78 °C had mp 59.5–61 °C: NMR δ 7.15 (AB q, $\Delta\nu_{1-3}$ = 59 Hz, J = 8.5 Hz, 2 H), 2.9 (s, 6 H), 2.8 (s, 6 H); IR (KBr) 2980–2810 (br) 2792, 1555, 1489, 1440, 1420, 1331, 1137, 974, 959, 820 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2S_5$: C, 37.24; H, 4.38. Found: C, 37.45; H, 4.66.

5g was prepared in 54% yield as for **5f** from **10g** (0.5 g, 2.4 mmol), sulfur (0.61 g, 2.4 mmol), and decalin (5 mL) at 185 °C for 1 h: mp 80–81.5 °C (hexane); NMR δ 7.9–7.75 (m, 1 H), 7.4–7.25 (m, 2 H), 4.05 (s, 2 H), 3.73 (s, 3 H); IR (KBr) 1738 cm^{-1}; exact mass calcd for $C_9H_8O_2S_5$ m/e 307.9126, observed 307.9111.

5h and **17h** were prepared in 55% combined yield as for **5f** from **10h** (0.3 g, 1.35 mmol), sulfur (0.35 g, 1.35 mmol), and decalin (5 mL) at 200 °C. The crude product was flash-chromatographed (2 × 8 in., hexane) to give first sulfur and then an ca. 1:1 mixture of **5h** and **17h**. GC/MS (OV 101 capillary column) identified the two components as m/e 322 (**5h**) and m/e 258 (**17h**): NMR (360 MHz) (**5h** and **17h** mixture) 7.8–7.75 (m, 1 H), 7.38–7.26 (m, 2 H), 4.64 and 4.6 (overlapping pair of quartets, J = 8 Hz, 1 H), 3.7 and 3.66 (pair of singlets, 3 H), 1.54 and 1.48 (pair of doublets, J = 8 Hz, 3 H). The complimentary pairs of NMR signals were of approximately equal intensity.

5i and **17i** were prepared in 25% combined yield as for **5f** from **10i** (0.25 g, 1.01 mmol), sulfur (0.26 g, 1.01 mmol), and 1,2,4-trichlorobenzene (5 mL) at 215 °C for 40 min. Flash chromatography (hexane) gave first sulfur and then 40 mg of a 10:90 mixture of **5i** and **17i**: NMR (**5i**) (360 MHz) δ 7.79 (d, J = 2 Hz, 1 H), 7.54 (d, J = 2 Hz, 1 H), 1.54 (s, 9 H), 1.32 (s, 9 H); NMR (**17i**) (360 MHz) 7.35 (d, J = 2 Hz, 1 H), 7.17 (d, J = 2 Hz, 1 H), 1.43 (s, 9 H), 1.29 (s, 9 H). The components were further identified by GC/MS (as above), m/e 260 (**17i**). The parent was not observed for **5i**.

Identification of 17c. 5c (20 mg) was dissolved in 10 mL of UV-grade hexane (Burdick & Jackson). HPLC analysis (Zorbax Sil, hexane) showed no equilibration after 8 h. Diethylamine (5 μL) was added, and **17c** and sulfur began forming immediately. After 2–3 h, the equilibrium was attained with the ratio of **5c** to **17c** of 46:54. **17c** was obtained as a solution in hexane by preparative HPLC (Zorbax Sil, hexane). Concentration of the solution gave a gummy material which only partially redissolved in hexane or methylene chloride. The UV spectrum is in Table III. **17c** was also identified by GC/MS, m/e 240.

17c could also be prepared by simply dissolving **5c** in methanol (up to 4 mg/mL). These solutions generally equilibrated over 2 h. By substituting CD_3OD for methanol, we were able to follow the reaction by ^{19}F NMR (−57.86 for **5c** and −62.59 for **17c**) and obtained an initial rate of 2.1 × 10^{-4} s^{-1} at 22.5 °C.

Identification of 17e. 5e (100 mg) was dissolved in hexane (100 mL), and diethylamine (50 μL) was added. The solution was stirred 6 days; then the components were separated by HPLC as above. In this manner, 50 mg of **5e** was recovered along with a hexane solution of **17e** which had the UV spectrum recorded in Table III and m/e 250.

Identification of 17g. 5g (50 mg) was dissolved in methanol (20 mL), and diethylamine (50 μL) was added. The solution was stirred 3 days at ambient temperature; then the components were separated by reverse-phase HPLC (Zorbax ODS, 10% water–methanol) to give a dilute solution of **17g** which had the UV spectrum reported in Table III and m/e 244.

8-(Carboxamido)isothiazolopentathiepin 18. 3 (3 g, 11.2 mmol) was dissolved in concentrated H_2SO_4 (75 mL) at 0 °C. After 2 h, the precipitate was filtered, washed with water and ether, and then azeotropically dried with refluxing benzene to give 3.2 g (94%) of **18** as a monohydrate: mp 170 °C dec., IR (KBr, μ) 2.98, 3.18, 6.05, 6.33, 6.74, 7.16, 7.61, 8.04, 8.93, 9.30, 9.98, 10.60, 11.75, 12.05, 12.59, 14.95.

Anal. Calcd for $C_4H_2N_2OS_6 \cdot H_2O$: C, 15.8; H, 1.32; S, 63.2. Found: C, 15.89; H, 1.32; S, 63.5.

Isothiazolopentathiepin-8-carboxylic Acid (19). 18 (21 g, 73.4 mmol) was added to concentrated H_2SO_4 (200 g) over 2 min via Gooch tubing with the temperature rising to 33 °C. The slurry was heated to 70 °C to effect dissolution; then the homogeneous orange mixture was chilled to 0 °C. Sodium nitrite (20 g, 290 mmol) in 100 mL of water was added over 1.5 h with the temperature maintained at 5–10 °C (red fuming). After stirring 10 min more, the solution was allowed to warm, with gentle frothing occurring at ca. 20 °C. The mixture was heated gradually to 90 °C until N_2 evolution ceased (N_2 evolution begins at 40 °C) and allowed to stand overnight. The reaction was poured into 1000 g of ice and stirred. The precipitate was filtered, washed with water, and air-dried to leave 10.2 g (51%) of **19** as a yellow solid. A 1-g sample recrystallized from 15 mL of HOAc had mp >159 °C (polymerized): exact mass calcd for $C_4HNO_2S_6$ m/e 286.8331, found 286.8328.

8-Carbomethoxyisothiazolopentathiepin 20. 19 (5.0 g, 17.4 mmol) was slurried in benzene (200 mL), and thionyl chloride (1.5 mL, 20.5 mmol) and DMF (10 drops) were added. The mixture was refluxed 15 h during which time **19** dissolved and reacted to give an orange solution containing the acid chloride which was used without purification.

Methanol (0.7 mL, 17.5 mmol) was dissolved in benzene (50 mL) and chilled to 5 °C. The acid chloride (above) was place in one addition funnel, and triethylamine (2.5 mL, 17.4 mmol) in benzene (150 mL) was placed in a second addition funnel. The acid chloride and amine solutions were added simultaneously at such a rate that the temperature did not exceed 5 °C (45-min addition). The mixture was allowed to warm to room temperature and stir 3 h; then it was filtered. The filtrate was concentrated and chromatographed on silica gel (100 g, benzene) to give 2.85 g, 54%, of **20**. The product was recrystallized from boiling heptane to give a yellow solid: mp 68–72 °C; NMR δ 3.95 (s, 3 H); IR (KBr, μ) 5.76, 6.76, 6.98, 7.55, 8.15 (br), 9.14, 10.37, 10.59, 12.40 (d) 13.1, 14.52; exact mass calcd for $C_5H_3NO_2S_6$ m/e 300.8488, found 300.8505.

***N,N*-Dimethyl-3,4-bis(methylthio)aniline (22j). 5j** (0.5 g, 1.79 mmol) was dissolved in 50 mL of THF, and ethanol (50 mL) was added. Sodium borohydride (0.34 g, 8.96 mmol) was added in portions over 5 min. After stirring 15 min, the H_2 evolution ceased, and water (10 mL) was added. The mixture was heated to 50 °C for 5 min, cooled to ambient temperature, and methyl iodide (0.62 mL, 10 mmol) was added. After 30 min of additional stirring, the solvent was evaporated, and the residue was partitioned between water and ether. The organic phase was washed with brine, dried over sodium sulfate, and concentrated to leave 0.39 g of yellow oil which was chromatographed on silica (50 g, 20% ether–hexane). This gave 0.33 g (86%) of **22j** as a clear yellow oil which solidified on standing. Recrystallization from ether–hexane gave hard yellow needles: mp 49–51 °C; NMR δ 7.22 (d, J = 9.3 Hz, 1 H), 6.49 (d, partially obscured, J = 2.9 Hz, 1 H), 6.4 (dd, partially obscured, J = 2.9, 9.3 Hz, 1 H), 2.95 (s, 6 H), 2.46 (s, 3 H), 2.38 (s, 3 H); IR (neat) 1583 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}NS_2$: C, 56.30; H, 7.09. Found: C, 56.69; H, 6.93.

22k was prepared by the above procedure as a clear pale-yellow oil (67%): IR (neat) 1448, 1430, 1029, 801 cm^{-1}; NMR δ 7.1 (s, 3 H), 2.46 (s, 3 H), 2.44 (s, 3 H), 1.4 (small impurity); exact mass calcd for $C_8H_9S_2Cl$ m/e 203.9834, found 203.9852.

4-Chloro-1,2-benzenedithiol (21k). 5k (0.64 g, 2.4 mmol) was dissolved in THF (50 mL), and ethanol (25 mL) was added. Sodium borohydride (0.88 g, 23 mmol) was added over 10 min followed by stirring for 3 h at ambient temperature. Tartaric acid was added to bring the solution to pH 4, and then the solvent was evaporated. The residue was partitioned between ether and water. The organic phase was washed with brine, dried over sodium sulfate, and concentrated. The crude product was Kugelrohr-distilled at 70–80 °C (0.15 mmHg) to give 0.19 g (49%) of **21k** as a white solid; mp 29.5–30.5 °C [lit.[30] mp 31 °C].

6-(Dimethylamino)-2,3-bis(carbomethoxy)benzo-1,4-dithiin (23j). 5j (100 mg, 0.358 mmol) and dimethyl acetylenedicarboxylate (0.22 mL, 1.79 mmol) were dissolved in methylene chloride (10 mL). Triphenylphosphine (0.28 g, 1.08 mmol) in methylene chloride (3 mL) was added dropwise over 10 min. After stirring 1 h at ambient temperature, the solvent was evaporated. The residue was purified by preparative TLC (silica gel, 25% ether/hexane, two elutions) to give 60 mg (51%) of **23j** as a yellow solid. Recrystallization from methanol gave **23j** as a bright-yellow solid: mp 75–77 °C; NMR 7.18 (d, J = 8.5 Hz, 1 H), 6.73 (d, J = 2.7 Hz, 1 H), 6.58 (dd, J = 8.5, 2.7 Hz, 1 H), 3.82 (s, 6 H), 2.92 (s, 6 H); IR (KBr) 1730, 1717, 1588 (m), 1246 cm^{-1}; exact mass calcd for $C_{14}H_{15}NO_4S_2$ m/e 325.0442, found 325.0411.

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Registry No. 3, 66393-25-7; **5b**, 96348-59-3; **5c**, 88888-99-7; **5d**, 88888-95-3; **5e**, 88888-98-6; **5f**, 96219-73-7; **5g**, 96348-60-6; **5h**, 96348-61-7; **5i**, 96348-62-8; **5j**, 88888-97-5; **5k**, 88888-94-2; **7**, 96348-63-9; **8a**, 55315-55-4; **8b**, 96348-64-0; **9a**, 63928-30-3; **9b**, 96348-65-1; **10f**, 96219-71-5; **10g**, 96348-66-2; **10h**, 96348-67-3; **10i**, 96348-68-4; **11a**, 89088-62-0; **11b**, 89088-63-1; **11c**, 89088-64-2; **12a**, 75641-04-2; **12b**, 96348-69-5; **12c**, 96348-70-8; **12d**, 79208-61-0; **15** (R = CF_3), 70001-71-7; **17c**, 96348-71-9; **17e**, 96348-72-0; **17g**, 96348-73-1; **17h**, 96348-74-2; **17i**, 96348-75-3; **18**, 66393-26-8; **19**, 66393-27-9; **19** (acid chloride), 67862-62-8; **20**, 66393-30-4; **21k**, 52821-52-0; **22j**, 2570-54-9; **22k**,

29690-15-1; **23j**, 96348-76-4; *o*-$C_6H_4(SH)_2$, 17534-15-5; 3,4-dibromothiophene, 3141-26-2; thiophene-3-thiol, 7774-73-4; thiophene-3,4-dithiol, 87207-45-2; 4-butylthiophene-3-thiol, 96348-77-5; dimethyl acetylenedicarboxylate, 762-42-5.

Supplementary Material Available: Atomic coordinates, thermal parameters, a complete listing of bond distances, bond angles and torsion angles for **3**, **7**, **12d**, **5b**, **15**, and S_8, and equipment and procedures for the synthesis of **9a** and **9b** and benzene-1,2-dithiol (41 pages). Ordering information is given on any current masthead page.

An Expeditious Synthesis of Resistomycin

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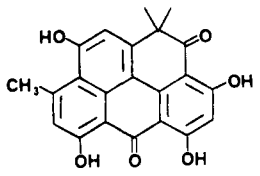
Contribution from the Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02167. *Received January 8, 1985*

Abstract: A five-step synthesis of resistomycin (**1**) from emodin (**3**) is described. The key step is the one-pot conversion **6** + **7** → **8** (eq 1). Mechanistic details of this reaction are reported; its regiochemistry can be reversed by changing reaction conditions.

The benzo[*cd*]pyrene ring system is an uncommon one. A survey[1] of the literature reveals that chemists have accorded it scant attention, perhaps because Nature evinces a similar disinterest. In fact, of the thousands of known natural substances, only two embody its carbon framework: the antibiotic resistomycin (**1**)[2] and its apparent oxidation product resistoflavin (**2**).[3]

A number[4] of research groups have launched synthetic assults on resistomycin, but to date only one effort[4c]—which employed an intramolecular Diels–Alder reaction of an isobenzofuran as



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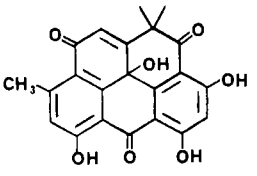

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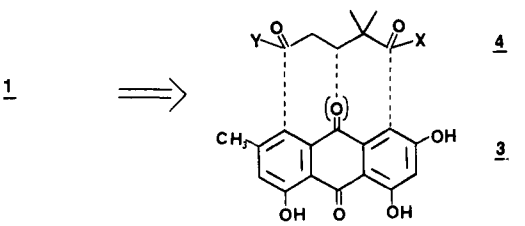
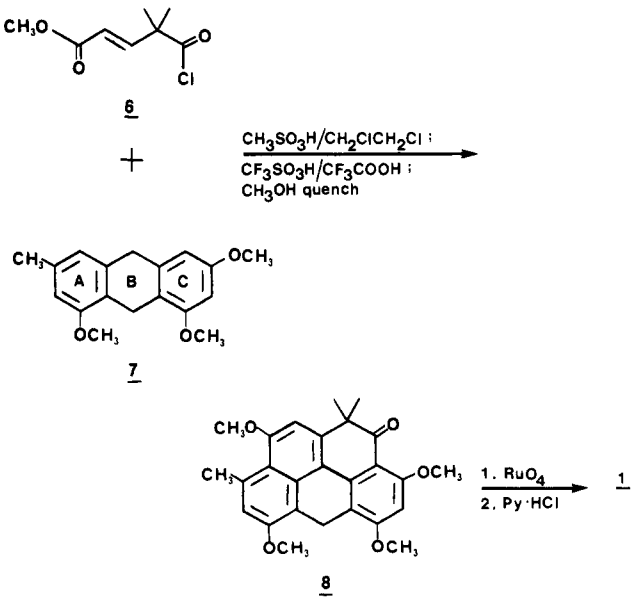
the key constructive step—has been capped by success. We now report an exceptionally brief synthesis based on an entirely different strategy.

Our approach was prompted by the exact correspondence between the bottom three rings of resistomycin and the structure of emodin (**3**), a widely occurring anthraquinone which is an article of commerce and is also readily available by isolation[5] or synthesis.[6]

Recognition of the similarity between resistomycin (**1**) and emodin (**3**) suggested that if one were able to achieve in effect the three connections indicated by the dotted lines linking **3** and **4**, then an expeditious route to resistomycin would emerge. This expectation has now been realized. Indeed, construction of the pentacyclic skelton can be accomplished in a one-pot operation (eq 1). The consequence is the fabrication of resistomycin from emodin in five steps.



Thus, successive exposure of a mixture of **6** and **7**—which are easily accessible as indicated in eqs 2 and 3—to CH_3SO_3H/CH_2ClCH_2Cl and then CF_3SO_3H/CF_3COOH followed by a



6 + **7** → **8** → **1** (1)

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