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Regioselective (Biomimetic) Synthesis of a Pentasulfane from *ortho*-Benzoquinone

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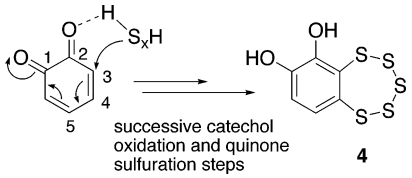


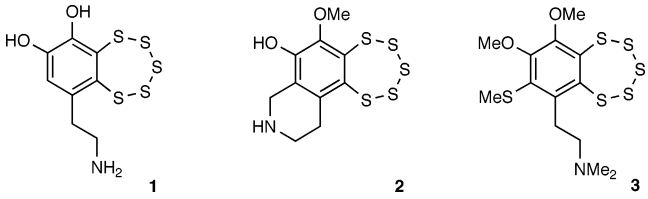
4

A mechanism is proposed for the formation of cyclic 5,6,7,8,9-pentathiabenzocycloheptene-1,2-diol, **4**, from the reaction of *o*-benzoquinone with reduced elemental sulfur, H_2S_x. 1,6-Conjugate addition to the quinone is favored over 1,4-conjugate addition. Hydrogen bonding to the quinone oxygen enhances the nucleophilicity of H_2S_x by facilitating the removal of the S−H proton. We propose that initially formed 3-polysulfidobenzene-diol intermediates are oxidized to their corresponding quinones and closure of the polysulfur ring subsequently takes place at the C3−C4 bond leading to **4**. A possible mechanism for the formation of the pentasulfur linkage in **4** is discussed, which is the key moiety found in a number of natural products.

Introduction

Desmethyl varacin (**1**), lissoclinotoxin B (**2**), and 5-(methylthio)varacin (**3**) represent a class of cytotoxic polysulfanes isolated from marine invertebrates (Scheme 1).[1−20] These compounds contain a dopamine core and a pentasulfur linkage.

SCHEME 1. Natural Polysulfanes



1 **2** **3**

Although natural benzopolysulfanes have been isolated,[1−10] the biosynthetic origin and mechanism for introduction of the sulfur atoms into dopamine have not been examined. Two reactions of sulfur and dopamine may relate to the biomimetic principles

(1) Compagnone, R. S.; Faulkner, D. J.; Carte, B. K.; Chan, G.; Hemling, M. A.; Hofmann, G. A.; Mattern, M. R. *Tetrahedron* **1994**, *50*, 12785−12792.
(2) Davidson, B. S.; Molinski, T. F.; Barrows, L. R.; Ireland, C. M. *J. Am. Chem. Soc.* **1991**, *113*, 4709−4710.
(3) Litaudon, M.; Guyot, M. *Tetrahedron Lett.* **1991**, *32*, 911−914.
(4) Davidson, B. S.; Ford, P. W.; Wahlman, M. *Tetrahedron Lett.* **1994**, *35*, 7185−7188.
(5) Litaudon, M.; Trigalo, F.; Martin, M.-T.; Frappier, F.; Guyot, M. *Tetrahedron* **1994**, *50*, 5323−5334.
(6) Ford, P. W.; Narbut, M. R.; Belli, J.; Davidson, B. S. *J. Org. Chem.* **1994**, *59*, 5955−60.
(7) Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1994**, *59*, 6600−6605.
(8) Guyot, M. *Pure Appl. Chem.* **1994**, *66*, 2223−2226.
(9) Ford, P. W.; Davidson, B. S.; Behar, V.; Danishefsky, S. J.; Stafford, J. A.; Feldman, P. L. *Chemtracts: Org. Chem.* **1994**, *7*, 242−246.
(10) Makarieva, T. N.; Stonik, V. A.; Dmitrenok, A. S.; Grebnev, B. B.; Iskov, V. V.; Rebachyk, N. M. *J. Nat. Prod.* **1995**, *58*, 254−258.
(11) Lee, A. H. F.; Chen, J.; Liu, D.; Leung, T. Y. C.; Chan, A. S. C.; Li, T. *J. Am. Chem. Soc.* **2002**, *124*, 13972−13973.
(12) Davis, R. A.; Sandoval, I. T.; Conception, G. P.; Moreira da Rocha, R.; Ireland, C. M. *Tetrahedron* **2003**, *59*, 2855−2859.
(13) Liu, H.; Pratasik, S. B.; Nishikawa, T.; Shida, T.; Tachibana, K.; Fujiwara, T.; Nagai, H.; Kobayashi, H.; Namikoshi, M. *Tetrahedron Lett.* **2004**, *45*, 7015−7017.
(14) Molinski, T. F. *Curr. Med. Chem. Anti-Infect. Agents* **2004**, *3*, 197−220.
(15) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W. *Chem. Rev.* **2004**, *104*, 2617−2630.
(16) Liu, H.; Pratasik, S. B.; Nishikawa, T.; Shida, T.; Tachibana, K.; Fujiwara, T.; Nagai, H.; Kobayashi, H.; Namikoshi, M. *Tetrahedron Lett.* **2004**, *45*, 7015−7017.
(17) Liu, H.; Fujiwara, T.; Nishikawa, T.; Mishima, Y.; Nagai, H.; Shida, T.; Tachibana, K.; Kobayashi, H.; Mangindaan, R. E. P.; Namikoshi, M. *Tetrahedron* **2005**, *61*, 8611−8615.
(18) Oda, T.; Fujiwara, T.; Liu, H.; Ukai, K.; Mangindaan, R. E. P.; Mochizuki, M.; Namikoshi, M. *Marine Drugs* **2005**, *3*, 15−21.
(19) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609−624.
(20) Rezanka, T.; Sobotka, M.; Spizek, J.; Sigler, K. *Anti-Infect. Agents Med. Chem.* **2006**, *5*, 187−224.

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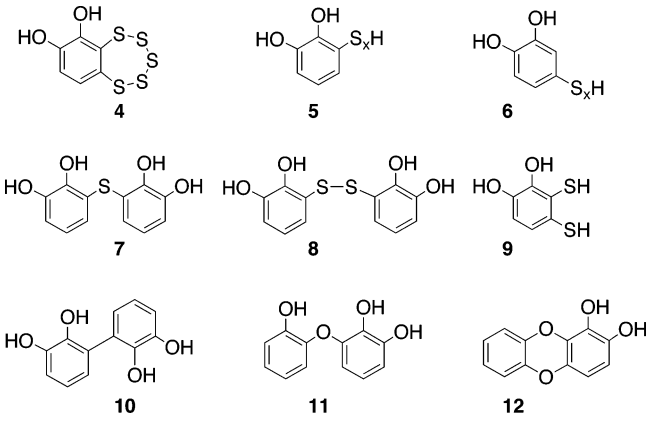
that underlie how benzopentathiepins arise biosynthetically. First, benzopentathiepins may arise from a two-electron transfer reaction of reduced elemental sulfur, H_2S_x, with dopamine-*o*-quinone. Second, benzopentathiepins may arise from a one-electron oxidation of dopamine followed by a reaction with neutral S_8. We have examined the viability of the first reaction in the laboratory generation of cyclic 5,6,7,8,9-benzopentathiepin-1,2-diol (**4**) using a *o*-benzoquinone−H_2S_x reaction. Our work with catechol [*o*-$C_6H_4(OH)_2$] served as a model for dopamine. A discussion is presented on the reaction of *o*-quinone and H_2S_x with specific interest in the mechanism of formation of pentasulfane **4**.

Results and Discussion

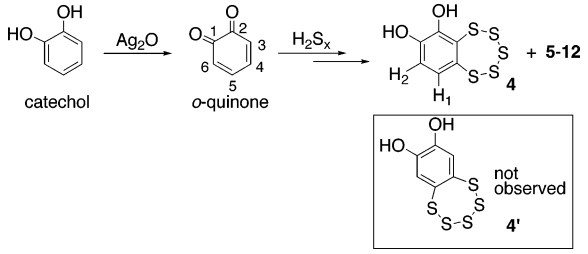
Reaction of Quinone with H_2S_x. The reaction of *o*-benzoquinone (180 mM) (generated in a reaction of Ag_2O with catechol in acetone)[21] with H_2S_x (3.9 M) (generated by sodium sulfide nonahydrate heated with elemental sulfur and precipitated with Cl_3CCO_2H)[22] was conducted by stirring for 1 h at room temperature. The red color of the quinone was rapidly converted to pale yellow on addition of H_2S_x. The reaction produced a series of products of high and low molecular weight. Precipitation of neutral elemental S_8 also accompanied the reaction. Polymeric and insoluble material was removed by filtration. GC/MS analysis revealed a large peak that is likely due to pentathiepin **4** (see Supporting Information). The GC/MS data are indicative of a pentathiepin [*m*/*z* = 64 (43), 96 (12), 110 (48), 142 (66), 204 (100), 268 (10)] because they display a weak molecular ion peak at *m*/*z* 268 [M^+] and a strong base peak at *m*/*z* 204 [$M^+ - 2S$] representing the loss of two sulfur atoms.[23] The M + 2 and M + 4 peaks caused by isotope ratios are as predicted. Another reaction product observed by GC/MS corresponded to 3-mercaptobenzene-1,2-diol (**5**, *x* = 1). However, attempts to purify the raw mixture by preparative TLC and HPLC were unsuccessful due to the high polarity of the compounds. Therefore, the hydroxy and thiol groups of the products were protected by acetylation with addition of DMAP (0.18 mmol) and acetic anhydride (2.52 mmol) in ethyl acetate. Ten products could then be chromatographically separated through preparative TLC and HPLC and characterized as the corresponding di-, tri-, or tetraacetates of **4**−**12** using ^1H and ^{13}C NMR and MS techniques (Scheme 2). Additional support for the structures assigned to **5** (*x* = 1), **6** (*x* = 1), **7**, and **8** came from their independent synthesis by the reaction of *o*-benzoquinone (18 mmol) with thioacetic acid (26 mmol) as described in the Supporting Information.

Of particular interest to us is the fact that **4** was formed in the quinone−H_2S_x reaction. The yield of **4** is low (3%), but it demonstrates the viability of the quinone−H_2S_x reaction in generating a benzopolysulfane. The quinone−H_2S_x reaction also gives byproducts, namely, 15% **5** (*x* = 1), 5% **6** (*x* = 1), 0.2% **7**, ∼1% **8**, and ∼2% **9**. Traces of known compounds **10**−**12** are observed (≤1%) (assigned on the basis of GC/MS analysis), which represent nucleophilic addition of catechol to the quinone. Acetylated **10**−**12** were obtained in higher yield (>5% total)

SCHEME 2. Compounds 4−12 Detected as the Corresponding Di-, Tri-, or Tetraacetates



SCHEME 3



in the absence of H_2S_x when quinone and catechol (1:1) were stirred in a 5% $NaHCO_3$ solution followed by a reaction with pyridine and acetic anhydride. Such nucleophilic additions to *o*-quinone are known.[21,26−30]

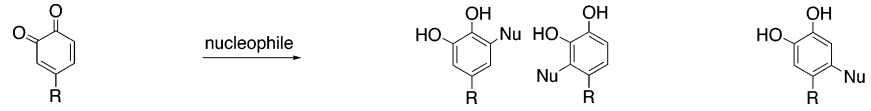
The NMR data pointed to diacetylated **4** not **4′** (Scheme 3). The ^1H NMR spectrum revealed two singlets corresponding to methyls of acetyl groups protecting two OH groups adjacent to each other at 2.31 and 2.35 ppm and two doublets for H_1 and H_2 of the aromatic ring with δ = 7.76 ppm and $^3J_{13}$ = 8.4 Hz and δ=7.18 ppm and $^3J_{13}$=8.4 Hz, respectively. The J_{13} coupling for **4** is comparable to that observed by Sato et al. for 6,7-dimethoxybenzopentathiepin (*J* = 8.4 Hz, 1H, ArH).[31] The regioselective formation of the polysulfur ring at the C3−C4 bond of *o*-benzoquinone and the predominance of sulfur products arising from *o*-quinone 1,6-conjugate addition (e.g, **5**, **7**, and **8**) were not immediately understandable. This regiochemical discrimination for closure of the polysulfur ring at the C3−C4 bond leading to **4** rather than the C4−C5 bond leading to **4′** is interesting, which led us to consider the mechanism of formation.

Mechanism of Formation of 4. A route is proposed to reach **4** from *o*-quinone and reduced elemental sulfur. The experimental and theoretical evidence that supports the mechanism outlined in Scheme 4 includes the following:

(1) H_2S_x is more likely to react at C3 of *o*-quinone compared to C4 because of possible carbonyl H-bonding in the former, which enhances the nucleophilicity of H_2S_x (Table 1, reaction

(21) Harley-Mason, J.; Laird, A. H. *J. Chem. Soc.* **1958**, 1718−1719.
(22) Steudel, R. *Top. Curr. Chem.* **2003**, *231*, 99−125.
(23) The GC/MS results for **4** are in agreement with the MS fragmentation pattern seen in other pentathiepins.[1,5,8,24,25]
(24) Brzostowska, E. M.; Greer, A. *J. Am. Chem. Soc.* **2003**, *125*, 396−404.
(25) Brzostowska, E. M.; Greer, A. *J. Org. Chem.* **2004**, *69*, 5483−5485.
(26) Klecka, G. M.; Gibson, D. T. *Biochem. J.* **1979**, *180*, 639−645.
(27) Forsyth, W. G. C.; Quesnel, V. C. *Biochim. Biophys. Acta* **1957**, *25*, 155−160.
(28) Forsyth, W. G. C.; Quesnel, V. C.; Roberts, J. B. *Biochim. Biophys. Acta* **1960**, *37*, 322−326.
(29) Kohler, H. E.; Schmid, A.; Maarel, M. *J. Bacteriol.* **1993**, *175*, 1621−1628.
(30) Homer, L.; Weber, K. H. *Ber.* **1963**, *96*, 1568−78.
(31) Sato, R.; Ohyama, T.; Ogawa, S. *Heterocycles* **1995**, *41*, 893−896.

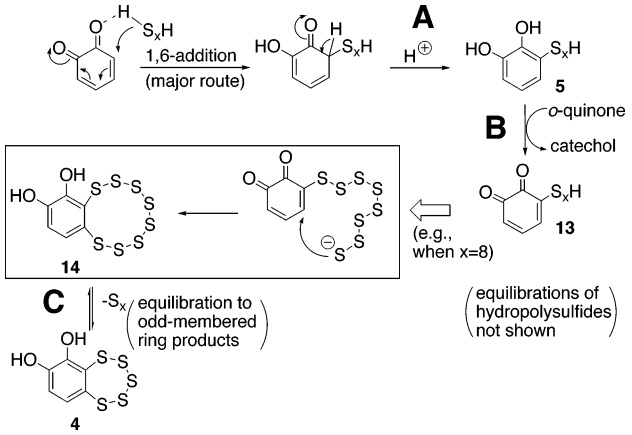
TABLE 1. Ratios of Catechol Products That Arise from Nucleophilic Addition to *o*-Benzoquinones



reaction	R	nucleophile	1,6-product(s)	1,4-product	ref
1	H	H_2S_x[a]	74	26	this work
2	H	$CH_3C(=O)SH$[b]	98	2	this work
3	$CH_2CH_2NH_2$	cysteine	∼100	–	[d]
4	$CH_2CH_2NH_2$	*N*-acetylcysteine	99	–	[e]
5	H	$CH_3C(=O)S^{\ominus}$[c]	–	∼100	this work
6	H or CH_3	1,2,4-triazolium-3-thiolate	–	∼100	[f]
7	CH_2CH_2NHAc	thiourea	–	∼100	[g]
8	H or CH_3	thiourea	–	80−90	[h]

[a] NMR detection of products formed in acetone-d_6 at 25 °C after addition of H_2S_x to *o*-benzoquinone. [b] NMR detection of products formed in CD_3Cl at 25 °C after addition of thioacetic acid to *o*-benzoquinone. [c] NMR detection of products formed in acetone-d_6 at 25 °C after addition of H_2S_x and 5% aqueous $NaHCO_3$ to *o*-benzoquinone. [d] Relative ratios were not reported; however, the 5-*S*-cysteinyl conjugate of dopamine is the predominant product. Ref 44. [e] At pH 2, the ratio of the two 1,6-products, 2-*S*-(*N*-acetylcysteinyl)dopamine to 5-*S*-(*N*-acetylcysteinyl)dopamine, is 10:89. A small amount of the di-1,6-adduct 2,5-*S*,*S*′-di(*N*-acetylcysteinyl)dopamine is also produced. Ref 45. A similar result is reported for reactions of *N*-acetyldopamine-*o*-quinone or *N*-*β*-alanyldopamine-*o*-quinone with *N*-acetylcysteine. Ref 47. [f] This mesoionic mercaptan adds to *o*-quinone and 4-methyl-*o*-quinone to form salt products. TsO^- is the counter salt. Ref 46. [g] Relative ratios were not reported; however, the 6-*S*-thiourea conjugate of *N*-acetyldopamine is the predominant product. A similar result is also reported for reactions of *N*-*β*-alanyldopamine-*o*-quinone with thiourea. Ref 47. [h] Based on isolated yields. The 1,6-products were not observed. Ref 48.

SCHEME 4. Mechanism of Closure of the Polysulfide Ring 4



1). As a consequence, 3- and 4-mercaptobenzene-1,2-diols [triacetylated **5** and **6** ($x = 1$)] are found in the product mixtures in a 74:26 ratio. The corresponding 3- and 4-hydrosulfidobenzene-1,2-diols [**5** and **6** ($x \geq 2$)] are assumed to be present but are unstable to isolation.[32] The regioselectivity of the H_2S_x addition to *o*-quinone is in the same direction as the addition of thioacetic acid (reaction 2). Thioacetic acid was added to an acetone solution containing 0.3 equiv of *o*-quinone and indicated a preference for the 1,6-addition product to the 1,4-addition product (98:2). Similar biological examples exist where 1,6-addition processes are favored, such as the reaction of cysteine with dopamine-*o*-quinone in the formation of 5-*S*-cysteinyldopamine, which is relevant to the mechanism underlying in vivo neuronal degeneration[37−41] (Parkinson's disease) (Table 1, reactions 3 and 4).[42−45] In contrast, thioacetic acid in the presence of 5% $NaHCO_3$ (reaction 5), triazolium thiolate (reaction 6),[46] and thiourea (reactions 7 and 8)[47,48] readily undergo 1,4-addition reactions to quinones because these sulfur nucleophiles lack an ionizable S−H proton so that H-bonding to the quinone oxygen cannot take place.[49]

(2) 3,4-Dimercaptobenzene-1,2-diol **9** is present in the quinone−H_2S_x reaction mixture. However, other related dimercaptobenzene-1,2-diol isomers are not observed. 4,5-Dimercaptobenzene-1,2-diol (**15**), 3,5-dimercaptobenzene-1,2-diol (**16**), and 3,6-dimercaptobenzene-1,2-diol (**17**) are not found to within the experimental error for their detection, ∼0.1 mM. The quinone−H_2S_x reaction contains a large excess of H_2S_x but does not show the production of the C3/C6 product **17**. A second 1,6-addition would have been expected with the anticipated regioselectivity to give **17**. Furthermore, we find that over the course of a few days the peak for **9** increases and concomitantly the magnitude of the peak for **4** decreases (Scheme 5), which is reminiscent of thiol−disulfide interconversions seen in many organic reactions and biological systems.[50] It is an important

(32) Hydropolysulfides (RS_xH) are unstable and usually cannot be directly detected because equilibration processes lead to a series of RSS_xSR products.[33−36]

(33) Argyropoulos, D. S.; Hou, Y.; Ganesaratnam, R.; Harpp, D. N.; Koda, K. *Holzforschung* **2005**, *59*, 124−131.

(34) Mitra, K.; Kim, W.; Daniels, J. S.; Gates, K. S. *J. Am. Chem. Soc.* **1997**, *119*, 11691−11692.

(35) (a) Chatterji, T.; Keerthi, K.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3921−3924. (b) Chatterji, T.; Keerthi, K.; Gates, K. S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1349−1352.

(36) (a) Behroozi, S. J.; Kim, W.; Gates, K. S. *J. Org. Chem.* **1995**, *60*, 3964−3966. (b) Sawwan, N.; Brzostowska, E. M.; Greer, A. *J. Org. Chem.* **2005**, *70*, 6968−6971.

(37) Tse, D. C. S.; McCreery, R. L.; Adams, R. N. *J. Med. Chem.* **1976**, *19*, 37−40.

(38) Hastings, T. G. *J. Neurochem.* **1995**, *64*, 919−924.

(39) Hastings, T. G.; Zigmond, M. J. *J. Neurochem.* **1994**, *63*, 1126−1132.

(40) Palumbo, A.; d'Ischia, M.; Misuraca, G.; Martino, L. D.; Prota, G. *Biochim. Biophys. Acta* **1995**, *1245*, 255−261.

(41) Napolitano, A.; Palumbo, A.; d'Ischia, M.; Prota, G. *J. Med. Chem.* **1996**, *39*, 5192−5201.

(42) Zhang, F.; Dryhurst, G. *Bioorg. Chem.* **1993**, *21*, 392−410.

(43) Zhang, F.; Dryhurst, G. *J. Med. Chem.* **1994**, *37*, 1084−1098.

(44) (a) Zhang, F.; Dryhurst, G. *Bioorg. Chem.* **1995**, *23*, 193−216. (b) Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J. *Chem. Res. Toxicol.* **2000**, *13*, 135−160.

(45) Xu, R.; Huang, X.; Kramer, K. J.; Hawley, M. D. *Bioorg. Chem.* **1996**, *24*, 110−126.

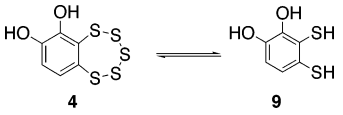
(46) Altland, H. W.; Briffa, B. F., Jr. *J. Org. Chem.* **1985**, *50*, 433−437.

(47) Huang, X.; Xu, R.; Hawley, M. D.; Hopkins, T. L.; Kramer, K. J. *Arch. Biochem. Biophys.* **1998**, *352*, 19−30.

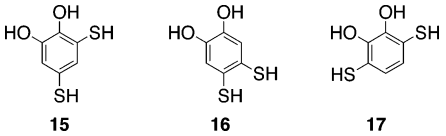
(48) Daneke, J.; Jahnke, U.; Pankow, B.; Wanzlick, H. W. *Tetrahedron Lett.* **1970**, *11*, 1271−72.

(49) Compounds **11** and **12** arise from a preferential 1,6-addition of a phenolic OH to *o*-quinone. This is in accord with the regioselective reaction seen for H_2S_x addition to *o*-quinone with a preferential 1,6-addition rather than a 1,4-addition.

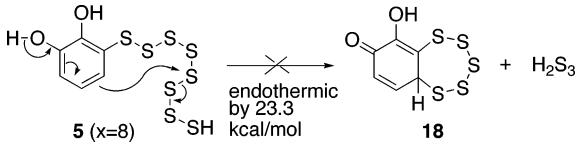
SCHEME 5



SCHEME 6. Compounds Not Observed in the Reaction



SCHEME 7. Unlikely Unimolecular Ring Closure Pathway



observation that **9** is derived from **4** in a decomposition process. Tri- and tetrasulfur addition products of quinone and H_2S_x are also not detected (Scheme 6).

(3) Control experiments show that there is no reaction between catechol and neutral S_8. Furthermore, a direct pathway to polysulfur ring closure of **5** ($x = 8$) is predicted to be endothermic and probably irrelevant to the chemistry to form **4** based on energetic demands (Scheme 7). B3LYP/6-31G(d) calculations were used to predict the energetics of the alternative cyclization of **5**, where $x = 8$. We compared the energy difference of **5** ($x = 8$) relative to 1-hydroxy-4a*H*-5,6,7,8,9-pentathiabenzocyclohepten-2-one (**18**) with H_2S_3. The control experiments with neutral S_8 and the computational results provide evidence that the new C−S bonds in **4**−**9** come only from reactions between quinones and reduced sulfur compounds.

The above data taken together provide support for the mechanism in Scheme 4. H_2S_x incorporates regioselectively into *o*-benzoquinone to give 3-hydrosulfidobenzene-1,2-diols **5** ($x = 1-8$). A second oxidation can then take place, where **5** is oxidized by unreacted *o*-benzoquinone producing **13** and catechol as a byproduct (Scheme 4B). Unimolecular attack of the polysulfur chain ion onto the C4 of **13** should occur at some point when the sulfur chain is sufficiently long, e.g., $x = 8$. Formation of **4** is consistent with an oxidation of 3-polysulfidobenzene-diols with a dependence on the chain length of the 3-polysulfidoquinone, thus leading to unimolecular ring closure. A subsequent equilibration between benzooctathiecin **14** and pentathiepin **4** (Scheme 4C) can be envisioned similar to the one observed previously in an *o*-benzyne−S_8 reaction.[25] The odd-membered *ortho*-benzofused polysulfane *o*-$(HO)_2C_6H_2S_x$ rings (except $x = 1$ which suffers from ring strain) are likely to possess enhanced conformational stability compared to the even-membered rings. Pentasulfane structures are quite common and often formed in polysulfur heterocycle syntheses.[51−62] Furthermore, the presence of nucleophiles can facilitate equilibria between **14** and stable **4**. Such nucleophile-dependent equilibria of polysulfane compounds[25,63−67] and difficulties in the isolation and purification of polysulfanes have been previously reported in the literature.[68,69]

An alternative mechanism that we deem unlikely is the bimolecular addition of H_2S_x with **5** ($x = 1-8$) (followed by subsequent ring closure). The absence of **15**−**17** provides an argument for a unimolecular ring closure by 3-polysulfidoquinone with subsequent formation of **4**. The absence of **15**−**17** in the reaction is probably due to the lesser efficiency of a bimolecular reaction of H_2S_x with **13**. The mechanistic conclusions may be reasonable even though it is difficult to know exactly what is taking place due to the many equilibration processes and possible intermediate radicals that may be present in the formation of the polysulfanes. The quinone−H_2S_x reaction is reminiscent of thiol chemistry reported in the literature based on formation of sulfur-containing adducts of catechols,[38−44] although the present work describes the formation of polysulfanes. Catechol-amines can undergo autoxidation yielding semiquinones, quinones, protonated superoxide ions, and H_2O_2 under aerobic conditions.[70−72] A competing 1,4-addition and radical addition reaction take place in the reaction of HS^- with the *p*-quinone-containing natural product juglone, where the radical addition is favored at higher pH.[73] We have not investigated whether radical scavengers influence the *o*-quinone−H_2S_x reaction.

Conclusion

The reaction of *o*-benzoquinone and H_2S_x leads to pentathiepin **4** and several byproducts. The proposed mechanism involves a unimolecular cyclization of 3-polysulfidoquinone intermediates **13**, e.g., where $x = 8$. It is likely that the quinone−H_2S_x reaction can be used to synthesize natural product

(50) Buckberry, L. D.; Teesdale-Spittle, P. H. Sulfur-Hydrogen Compounds. In *Biological Interactions of Sulfur Compounds*; Mitchel, S., Ed.; Taylor & Francis: London, 1996; pp 113−144.
(51) Amelichev, S. A.; Konstantinova, L. S.; Lyssenko, K. A.; Rakitin, O. A.; Rees, C. W. *Org. Biomol. Chem.* **2005**, *3*, 3496−3501.
(52) Amelichev, S. A.; Aysin, R. R.; Konstantinova, L. S.; Obruchnikova, N. V.; Rakitin, O. A.; Rees, C. W. *Org. Lett.* **2005**, *7*, 5725−5727.
(53) Muraoka, H.; Ogawa, S.; Nagahora, N.; Kawai, Y.; Sato, R. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 2026−2036.
(54) Janosik, T.; Stensland, B.; Bergman, J. *J. Org. Chem.* **2002**, *67*, 6220−6223.
(55) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W.; Souvorova, L. I.; Golovanov, D. G.; Lyssenke, K. A. *Org. Lett.* **2003**, *5*, 1939−1942.
(56) Konstantinova, L. S.; Rakitin, O. A.; Rees, C. W. *Chem. Commun.* **2002**, *11*, 1204−1205.
(57) Macho, S.; Rees, C. W.; Rodriguez, T.; Torroba, T. *Chem. Commun.* **2001**, 403−404.
(58) Steudel, R.; Hassenberg, K.; Pickardt, J. *Eur. J. Org. Chem.* **2001**, 2815−2817.
(59) Rewcastle, G. W.; Janosik, T.; Bergman, J. *Tetrahedron* **2001**, *57*, 7185−7189.
(60) Steudel, R.; Hassenberg, K.; Munchow, V.; Schumann, O.; Pickardt, J. *Eur. J. Inorg. Chem.* **2000**, *921*.
(61) Hou, Y.; Abu-Yousef, I. A.; Harpp, D. N. *Tetrahedron Lett.* **2000**, *41*, 7809−7812.
(62) Ishii, A.; Nakayama, J. *Rev. Heteroat. Chem.* **1998**, *19*, 1−34.
(63) Nakayama, J.; Akimoto, K. *Sulfur Rep.* **1994**, *16*, 61−111.
(64) Steudel, R. *Chem. Rev.* **2002**, *102*, 3905−3946.
(65) Sato, R. *Heteroat. Chem.* **2002**, *13*, 419−423.
(66) Lee, W. K.; Liu, B.; Park, C. W.; Shine, H. J.; Guzman-Jimenez, I. Y.; Whitmire, K. H. *J. Org. Chem.* **1999**, *64*, 9207.
(67) Mahling, S.; Asmus, K.-D.; Glass, R. S.; Hojjatie, M.; Wilson, G. S. *J. Org. Chem.* **1987**, *52*, 3717−3724. Erratum: Mahling, S.; Asmus, K.-D.; Glass, R. S.; Hojjatie, M.; Sabahi, M.; Wilson, G. S. *J. Org. Chem.* **1988**, *53*, 5192−5192.
(68) Harpp, D. N.; Smith, R. A. *J. Org. Chem.* **1979**, *44*, 4140−4144.
(69) Derbesy, G.; Harpp, D. N. *Tetrahedron Lett.* **1994**, *35*, 5381−5384.
(70) Richter, H. W.; Waddell W. H. *J. Am. Chem. Soc.* **1983**, *105*, 5434−5440.
(71) Terland, O.; Flatmark, T.; Tangeras, A.; Groenberg, M. *J. Mol. Cell. Cardiol.* **1997**, *29*, 1731−1738.
(72) Senoh, S.; Creveling, C. R.; Udenfriend, S.; Witkop, B. *J. Am. Chem. Soc.* **1959**, *81*, 6236−6240.
(73) Perlinger, J. A.; Kalluri, V. M.; Venkatapathy, R.: Angst, W. *Environ. Sci. Technol.* **2002**, *36*, 2663−2669.

polysulfanes. We are currently exploring dopamine-*o*-quinone as an intermediate in an H_2S_x reaction to generate polysulfane **1**.

Experimental Section

5,6,7,8,9-Pentathiabenzocycloheptene-1,2-diol (4) was separated by preparative silica gel TLC, $R_f = 0.5$ EtOAc/hexanes (1:3). Mass spectrum (EI): m/z = 64 (43), 96 (12), 110 (48), 142 (66), 204 (100), 268 (10).

Acetic Acid 2-Acetoxy-5,6,7,8,9-pentathiabenzocyclohepten-1-yl Ester or "Diacetylated 4". Yield 0.0007 g. Silica gel TLC, $R_f = 0.4$ (THF/hexanes, 1:3). ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.35 (s, 3H), 7.18 (d, 1H, $J = 8.4$ Hz), 7.76 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6, 117.8, 124.8, 125.5, 133.7, 142.5, 144.5, 167.7, 167.8. UV (CH_2Cl_2) λ_{max} 232 nm. Mass spectrum (EI): m/z = 64 (23), 102 (10), 131 (21), 139 (15), 172 (6), 204 (100), 246 (34), 288 (26), 352 (0.9). Peaks at 246 and 204 represent the loss of two ketene $CH_2{=}C{=}O$ fragments.

3-Mercaptobenzene-1,2-diol (5). ^{1}H NMR (acetone-d_6) δ 4.03 (s, 1H), 6.60 (t, $J = 7.82$ Hz, 1H), 6.66 (dd, $J = 1.6$, 7.8 Hz, 1H), 6.74 (dd, $J = 1.6$, 7.8 Hz, 1H), 7.76 (s, 1H), 8.50 (s, 1H).

Acetic Acid 2-Acetoxy-3-acetylsulfanyl-phenyl Ester or "Triacetylated 5". Yield 0.0006 g. Triacetylated **5** was isolated from silica gel TLC, $R_f = 0.42$ (EtOAc/hexanes, 1:3), from the quinone−H_2S_x reaction or via recrystallization in chloroform as white crystals (mp 80−83 °C) from the quinone−thiolacetic acid reaction (method 1, Supporting Information). The ^{1}H NMR spectrum of triacetylated **5** shows three singlets corresponding to methyls of the acetyl groups on two OH and SH groups adjacent to each other at 2.27, 2.29, and 2.41 ppm, respectively. ^{1}H NMR (acetone-d_6) δ 2.27 (s, 3H), 2.29 (s, 3H), 2.41 (s, 3H), 7.37−7.46 (m, 3H). ^{13}C NMR (acetone-d_6) δ 20.2, 20.3, 30.1, 124.6, 126.4, 134.5, 144.6, 168.1, 168.5, 192.0. IR (KBr) ν 1765, 1703, 1466, 1368, 1262, 1213, 1005 cm^{-1}. Mass spectrum (EI): m/z = 83 (2), 96 (1), 113 (2), 142 (100, M-3Ac), 184 (55, M-2Ac), 226 (27, M-Ac), 268 (8). HRMS calcd for $C_{12}H_{12}O_5S$ $(M + H)^+$ 269.0478, found 269.0476.

4-Mercaptobenzene-1,2-diol (6). ^{1}H NMR (acetone-d_6) δ 3.10 (s, 1H), 6.68 (dd, $J = 2.1$, 8.2 Hz, 1H), 6.73 (d, $J = 8.2$ Hz, 1H), 6.84 (d, $J = 2.1$ Hz, 1H), 8.03 (s, 1H), 7.93 (s, 1H).

Acetic Acid 2-Acetoxy-5-acetylsulfanyl-phenyl Ester or "Triacetylated 6". Prepared from the quinone−H_2S_x reaction and the quinone−thiolacetic acid reaction (method 2). Purification was accomplished by column chromatography using EtOAc/hexanes (1:4). Yellow crystals were obtained (mp 79−82 °C). ^{1}H NMR (acetone-d_6) δ 2.47 (s, 3H), 2.48 (s, 3H), 2.62 (s, 3H), 7.49 (d, $J = 8.4$ Hz, 1H), 7.51 (s, 1H), 7.54 (dd, $J = 2.1$, 8.4 Hz, 1H). ^{13}C NMR (acetone-d_6) δ 19.5, 19.5, 29.2, 124.0, 126.0, 129.3, 132.6, 142.4, 143.3, 168.0, 193.0. IR (KBr) ν 1773, 1752, 1703, 1491, 1364 cm^{-1}. Mass spectrum (EI): m/z = 268 (7), 226 (39, M-Ac), 184 (48, M-2Ac), 142 (100, M-3Ac). HRMS calcd for $C_{12}H_{12}O_5S$ $(M + H)^+$ 269.0478, found 269.0478.

Acetic Acid 2-Acetoxy-6-(2,3-diacetoxy-phenylsulfanyl)-phenyl Ester or "Tetraacetylated 7". Yield 0.0012 g. Silica gel TLC $R_f = 0.48$ (2:3 EtOAc/hexanes). ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.29 (s, 3H), 7.12−7.16 (m, 2H), 7.44 (dd, $J = 8.0$ Hz, $J = 1.5$ Hz, 1H). UV (CH_2Cl_2) λ_{max} 280, 321 nm. Mass spectrum (EI): m/z = 110 (20), 142 (11), 250 (100, M-4Ac), 292 (60, M-3Ac), 334 (41, M-2Ac), 376 (19, M-Ac), 418 (12).

Acetic Acid 2-Acetoxy-3-(2,3-diacetoxy-phenyldisulfanyl)-phenyl Ester or "Tetraacetylated 8". Yield 0.0048 g. Silica gel TLC $R_f = 0.42$ (2:3 EtOAc/hexanes). ^{1}H NMR (acetone-d_6) δ 2.28 (s, 6H), 2.30 (s, 6H), 7.25 (dd, $J = 1.5$, 7.3 Hz, 2H), 7.34 (t, $J = 7.3$ Hz, 2H), 7.51 (dd, $J = 1.5$, 7.3 Hz, 2H). ^{13}C NMR (acetone-d_6) 20.1, 20.5, 124.5, 127.8, 131.7, 142.0, 144.4, 168.2, 168.6. UV (CH_2Cl_2) λ_{max} 280, 320 nm. Mass spectrum (EI): m/z = 83 (6), 111 (10), 142 (71), 184 (22), 282 (100, M-4Ac), 324 (60, M-3Ac), 366 (91, M-2Ac), 408 (29, M-Ac), 450 (41). HRMS calcd for $C_{20}H_{18}O_8S_2$ $(M + NH_4)^+$ 468.0781, found 468.0784.

3,4-Dimercapto-benzene-1,2-diol or "Tetraacetylated 9". ^{1}H NMR 400 MHz (acetone-d_6) δ 2.30 (s, 3H), 2.31 (s, 3H), 2.42 (s, 3H), 2.42 (s, 3H), 7.22 (d, $J = 8.7$ Hz, 1H), 7.40 (d, $J = 8.7$ Hz, 1H). Mass spectrum (EI): m/z = 342 (3), 300 (44, M-Ac), 258 (55, M-2Ac), 216 (70, M-3Ac), 174 (100, M-4Ac).

Acetic Acid 3,2′,3′-Triacetoxy-biphenyl-2-yl Ester or "Tetraacetylated 10". Catechol acts as an ambident nucleophile in a reaction between the carbanion tautomer of catechol and *o*-quinone. Mass spectrum (EI): m/z = 386, 344 (M-Ac), 302 (M-2Ac), 260 (M-3Ac), 218 (M-4Ac).

Acetic Acid 2-(3,4-Diacetoxy-phenoxy)-phenyl Ester or "Triacetylated 11". Mass spectrum (EI): m/z = 344, 302 (M−Ac), 260 (M-2Ac), 218 (M-3Ac).

Acetic Acid 1-Acetoxy-dibenzo[1,4]dioxin-2-yl Ester or "Diacetylated 12". Mass spectrum (EI): m/z = 300, 258 (M−Ac), 216 (M-2Ac).

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Note Added after ASAP Publication. In the text, "[*o*-$C_6H_4(OH)_2$]" was incorrectly displayed as "[*o*-$C_6H_4(HO)_2$]" and "ambident" was spelled "ambient" in the version published ASAP March 23, 2007; the corrected version was published March 27, 2007.

Supporting Information Available: Experimental procedures and spectroscopic data for new compounds **4**−**9** and HRMS data for **5**, **6**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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