

Antimalarial Sulfone Trioxanes

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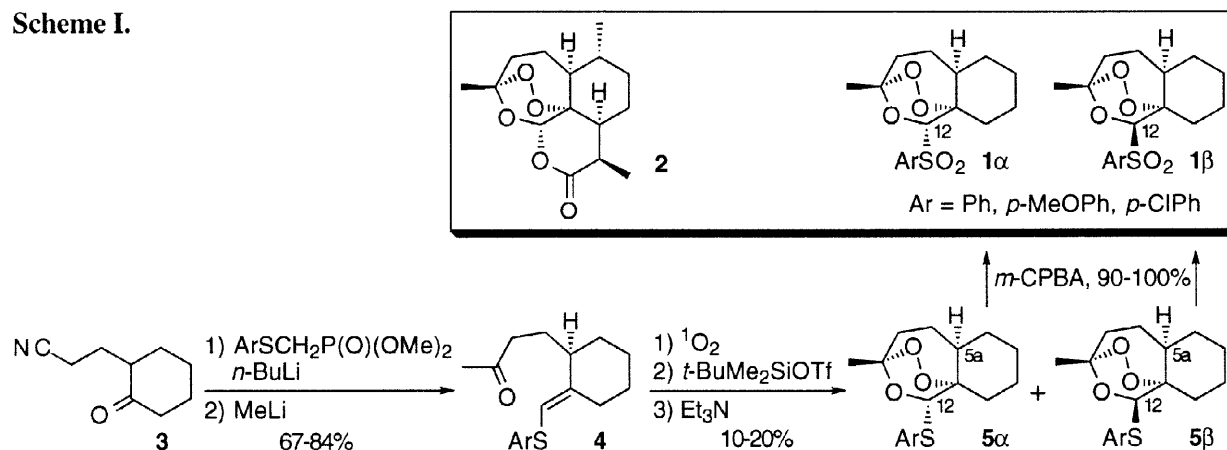
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Received 18 December 1997; revised 27 January 1998; accepted 29 January 1998

Abstract: A series of new sulfide and sulfone 1,2,4-trioxanes was prepared in only a few steps from commercial reactants. The sulfone trioxanes were found to have higher *in vitro* antimalarial potencies than the sulfides, with 12 β -arylsulfone trioxanes **1** β being from 1/3 to 1/4 as potent as the complex natural antimalarial trioxane artemisinin (**2**). A tentative chemical mechanism is proposed to account for the great difference in antimalarial activity of the 12 α - vs. 12 β -sulfide trioxanes.
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As part of our continuing research program to design and synthesize simple organic antimalarial peroxides,¹ we report here on a new series of 12-sulfonyl trioxanes **1**. These trioxanes are structurally simplified versions of the recently discovered and clinically effective Chinese antimalarial drug artemisinin (qinghaosu, **2**) that is a complex natural sesquiterpene lactone trioxane.² Although much structure-activity relationship (SAR) work has been done by others³ and by us^{1d} to define those structural and electronic features that would make new trioxanes potent antimalarials, no sulfone trioxanes have been reported. The non-peroxidic diaryl sulfone dapsone, however, is a clinically used antimalarial.⁴ Also, recent research has produced some new, antimalarially potent sulfone endoperoxides.⁵ We synthesized sulfone trioxanes **1** in the convergent manner shown in Scheme I.

Scheme I.



As shown in Scheme I, deprotonation of dimethyl arylthiomethanephosphonates (prepared *via* Arbuzov reactions of the corresponding chloromethyl aryl sulfides and trimethyl phosphite) with *n*-butyllithium and then reaction with cyanoethylcyclohexanone **3** followed by methyl lithium addition to the nitrile group gave methyl ketone vinyl sulfides **4** as separable mixtures of *Z*- and *E*-isomers.^{1a} Exposure to photochemically-generated singlet molecular oxygen followed by *t*-butyldimethylsilyl triflate then gave anomeric sulfide trioxane diastereomers **5** α and **5** β that were separated easily by column chromatography, and their relative C-12 stereochemistry was assigned by ¹H NMR spectroscopy, applying general rules that we described recently.⁶ For example, the 12 β -

phenyl diastereomer showed at δ 5.57 a characteristic W-coupling ($J = 1.6$ Hz) between the C-12 thioacetal hydrogen atom and the angular C-5a angular hydrogen atom, whereas the 12 α -phenyl diastereomer showed a sharp singlet for the thioacetal hydrogen atom at about δ 5.63. Separate oxidation of each of the vinyl sulfide trioxanes **5 α** and **5 β** with *meta*-chloroperbenzoic acid gave the corresponding target sulfone trioxanes **1 α** and **1 β** as crystalline solids that are thermally stable even at 60 °C for 24 hours.⁷

Antimalarial testing *in vitro* using our previously described protocol⁸ gave the results summarized in Table I. Several generalizations emerge, as follows: (1) although all of the 12 α -sulfide trioxanes are inactive, all of the 12 β -sulfide diastereomers are quite active; (2) all of the sulfone trioxanes are active antimalarials; (3) the 12 β -sulfones generally are somewhat more potent than the 12 α -anomers; and (4) 12 β -(*p*-chlorophenyl)sulfone **1 β** ($IC_{50} = 23$ nM) is almost 1/3 as potent an antimalarial as the complex natural trioxane artemisinin ($IC_{50} = 8.5$ nM).

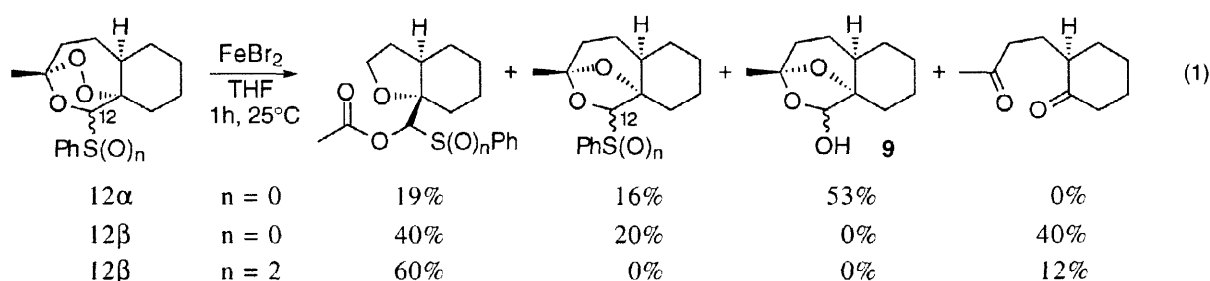
Table I. Chemical Structure-Antimalarial Activity Relationships in Chloroquine-Sensitive *P. falciparum* (NF54) Parasites *in Vitro*^a

trioxane	Z	Ar	C ₁₂ -ZAr stereochemistry	IC ₅₀ (nM)
5β	S	Ph	β	56
5α			α	>2500
1β	SO ₂	Ph	β	33
1α			α	59
5β	S	<i>p</i> -MeOPh	β	89
5α			α	>2500
1β	SO ₂	<i>p</i> -MeOPh	β	30
1α			α	43
5β	S	<i>p</i> -ClPh	β	110
5α			α	>2500
1β	SO ₂	<i>p</i> -ClPh	β	23
1α			α	25
Artemisinin				8.5

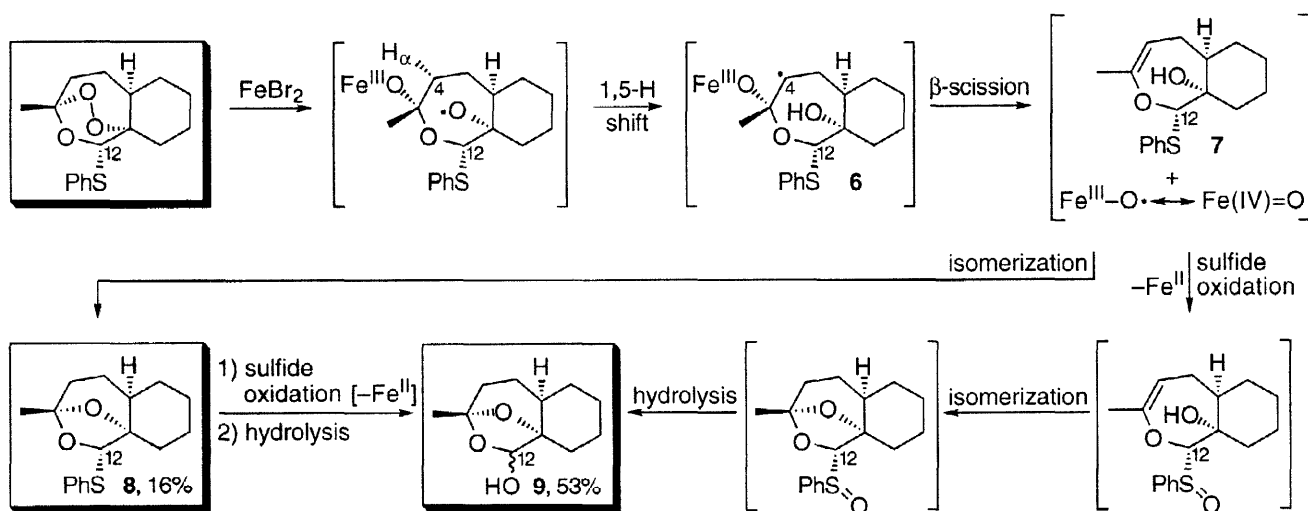
^aAntimalarial activity was determined as reported previously⁸. The standard deviation for each set of quadruplicates was $\leq 32\%$ of the mean. R^2 values for the fitted curves were ≥ 0.981 .

Following our previously described mechanistic studies⁹ involving iron(II)-induced degradation of such trioxanes to mimic the biological triggering of artemisinin by heme,^{9a} we exposed several of these new sulfide and sulfone trioxanes to ferrous bromide (Scheme II). For the pair of anomeric phenyl sulfides, the formation of lactol **9** or of a 1,5-diketone depended on the sulfide stereochemistry: the 12 α -sulfide gave substantial amounts of lactol **9** but no diketone, whereas the 12 β -sulfide gave no lactol but substantial amounts of 1,5-diketone. Formation of a 1,5-diketone product has been observed and rationalized previously,¹⁰ but lactol formation in the case of the 12 α -sulfide is unusual especially because the original C-12-sulfur atom has been replaced by an hydroxyl group. A plausible mechanistic pathway to account for lactol formation involves β -scission of Fe(III)–O• from the α -face of C₄-radical intermediate **6** (Scheme II), followed immediately by its oxidation of the α -oriented sulfide sulfur atom;

we have previously shown that such an intermediate high-valent iron-oxo species is capable of oxidizing methyl phenyl sulfide into methyl phenyl sulfoxide.^{9a} Alternatively, isomerization of hydroxy enol ether **7** into cyclic sulfide **8** might then be followed by sulfide $\rightarrow$ sulfoxide oxidation by the high-valent iron-oxo species still residing close to the α -face of the organic molecule (note that 12 β -oriented sulfide trioxane does not form any lactol product). Finally, ferrous ion-promoted hydrolysis of the C₁₂-sulfinyl monothioacetal functional group^{11,12} then could reasonably form the observed lactol **9**, isolated as a single diastereomer (C₁₂-stereochemistry not reliably assigned). Whatever the exact sequence of these reactions actually is, this tentative mechanistic proposal is consistent with the 12 α -sulfide being antimalarially inactive based on the rapid interception and reduction of the highly oxidizing and likely cytotoxic high-valent iron-oxo intermediate species;^{9a} when this 12 α -sulfide trioxane reacted with ferrous bromide in the presence of hexamethyl Dewar benzene (HMDB), no rearrangement into hexamethylbenzene was observed, whereas the same reaction using the corresponding antimalarially potent 12 α -sulfone (the sulfone sulfur atom being unable to reduce any iron-oxo intermediate) did show substantial formation of hexamethylbenzene, implicating the intermediacy of a reactive high-valent iron-oxo species.



Scheme II.



In summary, these SAR generalizations and mechanistic considerations, which support the importance of intermediate high-valent iron-oxo species for high antimalarial activity, may help in the design of other potent antimalarial trioxanes for effective use in the worldwide fight against malaria.

Acknowledgment: We thank the NIH (AI-34885 and NCRR OPD-GCRC RR00722) and the Burroughs Wellcome Fund for financial support.

References

1. (a) Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *Heteroatom Chem.* **1995**, *6*, 105; (b) Posner, G. H.; Wang, D.; González, L.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron Lett.* **1996**, *37*, 815; (c) Posner, G. H.; Tao, X.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Ibid.* **1996**, *37*, 7225; (d) Cumming, J. N.; Ploypradith, P.; Posner, G. H. *Adv. Pharmacol.* **1997**, *37*, 253; (e) Woo, S. H.; Parker, M. H.; Ploypradith, P.; Northrop, J.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39* (No. 13), 000.
2. Zhou, W.-S.; Xu, X.-X. *Acc. Chem. Res.* **1994**, *27*, 211.
3. (a) Acton, N.; Karle, J. M.; Miller, R. E. *J. Med. Chem.* **1993**, *36*, 2552; (b) Boukouvalas, J.; Pouliot, R.; Fréchette, Y. *Tetrahedron Lett.* **1995**, *35*, 4167; (c) Jefford, C. W.; Kohmoto, S.; Jaggi, D.; Timári, G.; Rossier, J.-C.; Rudaz, M.; Barbuzzi, O.; Gérard, D.; Burger, U.; Kamalaprija, P.; Mareda, J.; Bernardinelli, G.; Manzanares, I.; Canfield, C. J.; Fleck, S. L.; Robinson, B. L.; Peters, W. *Helv. Chim. Acta* **1995**, *78*, 647; (d) Abouabdellah, A.; Bégué, J.-P.; Bonnet-Delpon, D.; Gantier, J.-C. *Bioorg. Med. Chem.* **1996**, *6*, 2717; (e) Vroman, J. A.; Khan, I.; Avery, M. A. *Synlett* **1997**, 1438; (f) Jung, M. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1091; (g) McKonnen, B.; Ziffer, H. *Tetrahedron Lett.* **1997**, *38*, 731; (h) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73; (i) Paitayatat, S.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. *J. Med. Chem.* **1997**, *40*, 633; (j) Ziffer, H.; Hight, R. J.; Klayman, D. L. *Progr. Chem. Nat. Org. Prod.* **1997**, *72*, 123.
4. (a) Rosenthal, P. J.; Olson, J. E.; Lee, G. K.; Palmer, J. T.; Klaus, J. L.; Rasnick, D. *Antimicrob. Agents. Chemother.* **1996**, *40*, 1600; (b) see also, Tripathi, R. C.; Saxena, M.; Chandra, S.; Saxena, A. K. *Ind. J. Chem.* **1995**, *34(B)*, 164.
5. Bachi, M. D.; Korshin, E.; Ploypradith, P.; Cumming, J. N.; Xie, S.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.*, in press.
6. Oh, C. H.; Wang, D.; Cumming, J. N.; Posner, G. H. *Spectrosc. Lett.* **1997**, *30*, 241.
7. All new compounds were characterized spectroscopically and by combustion analysis or by high resolution mass spectrometry.
8. Posner, G. H.; González, L.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A. *Tetrahedron* **1997**, *53*, 37.
9. (a) Posner, G. H.; Cumming, J. N.; Ploypradith, P.; Oh, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 5885; (b) Bloodworth, A. J.; Shah, A. *Tetrahedron Lett.*, **1995**, *36*, 7551; (c) Wu, W.-M.; Yal, Z.-J.; Wu, Y.-L.; Jiang, K.; Wang, J.-F.; Wang, Y.-F.; Chen, H.-B.; Shan, F.; Li, Y. *Chem. Commun.* **1996**, 2213; (d) O'Neill, P. M.; Bishop, L. P.; Searle, N. L.; Maggs, J. L.; Ward, S. A.; Bray, P. G.; Storr, R. C.; Park, B. K. *Tetrahedron Lett.* **1997**, *38*, 4263.
10. Posner, G. H.; Park, S. B.; González, L.; Wang, D.; Cumming, J. N.; Klinedinst, D.; Shapiro, T. A.; Bachi, M. D. *J. Am. Chem. Soc.* **1996**, *118*, 3537.
11. (a) Shi, X.-X.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 4331; (b) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756; (c) Takahashi, T.; Nakamura, C. Y.; Satoh, J. Y. *J. Chem. Soc., Chem. Comm.* **1977**, 680. See also Hirano, M.; Ukawa, K.; Yakabe, S.; Clark, J. H.; Morimoto, T. *Synthesis* **1997**, 858.
12. As a model system, monothioacetal **i** and its corresponding sulfoxide **ii** and sulfone **iii** were prepared. Their relative rates of ferrous bromide-promoted hydrolysis in aqueous THF are **ii** >> **i** $\approx$ **iii**. Virtually no hydrolysis of sulfoxide **ii** occurred at r.t. for 1 h, however, in the **absence** of FeBr₂.

