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Antimalarial Sulfone Trioxanes

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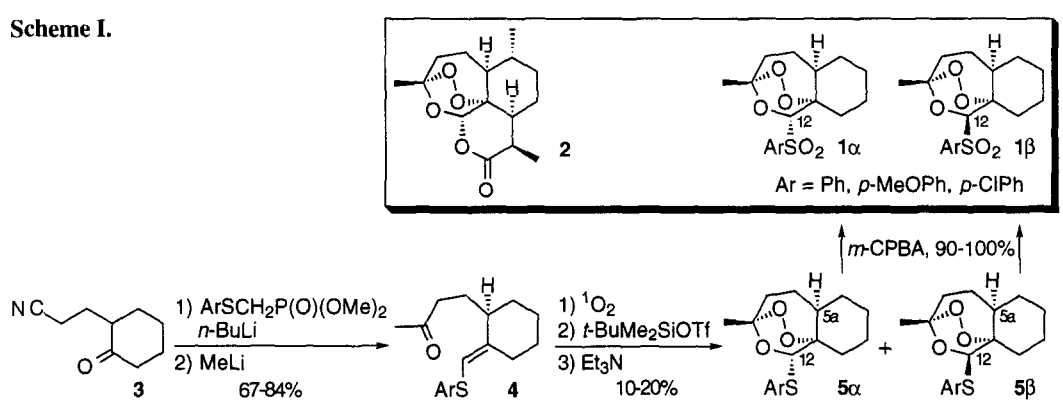
Abstract: A series of new sulfide and sulfone 1,2,4-trioxanes was prepared in only a few steps from commercial reactants. The sulfone trioxanes were found to have higher *in vitro* antimalarial potencies than the sulfides, with 12β-arylsulfone trioxanes **1β** being from 1/3 to 1/4 as potent as the complex natural antimalarial trioxane artemisinin (**2**). A tentative chemical mechanism is proposed to account for the great difference in antimalarial activity of the 12α- *vs.* 12β-sulfide trioxanes.

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 others[3] 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 methyllithum 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 **5α** and **5β** that were separated easily by column chromatography, and their relative C-12 stereochemistry was assigned by ^{1}H NMR spectroscopy, applying general rules that we described recently.[6] For example, the 12β-

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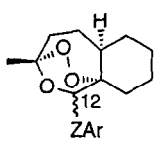
phenyl diastereomer showed at δ 5.57 a characteristic W-coupling (J = 1.6 Hz) between the C-12 thioacetal hydrogen atom and the angular C-5a angular hydrogen atom, whereas the 12α-phenyl diastereomer showed a sharp singlet for the thioacetal hydrogen atom at about δ 5.63. Separate oxidation of each of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

Antimalarial testing *in vitro* using our previously described protocol[8] gave the results summarized in Table I. Several generalizations emerge, as follows: (1) although all of the 12α-sulfide trioxanes are inactive, all of the 12β-sulfide diastereomers are quite active; (2) all of the sulfone trioxanes are active antimalarials; (3) the 12β-sulfones generally are somewhat more potent than the 12α-anomers; and (4) 12β-(*p*-chlorophenyl)sulfone **1β** (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]

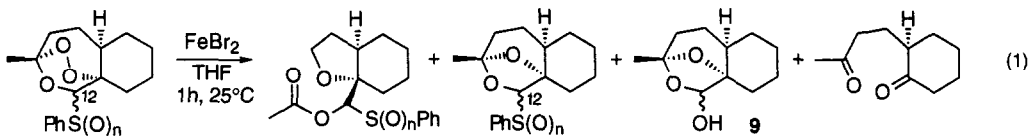


trioxane	Z	Ar	C_{12}-ZAr stereochemistry	IC_{50} (nM)
5β	S	Ph	β	56
5α			α	>2500
1β	SO_2	Ph	β	33
1α			α	59
5β	S	*p*-MeOPh	β	89
5α			α	>2500
1β	SO_2	*p*-MeOPh	β	30
1α			α	43
5β	S	*p*-ClPh	β	110
5α			α	>2500
1β	SO_2	*p*-ClPh	β	23
1α			α	25
Artemisinin				8.5

[a]Antimalarial activity was determined as reported previously[8]. The standard deviation for each set of quadruplicates was ≤ 32% of the mean. R^2 values for the fitted curves were ≥ 0.981.

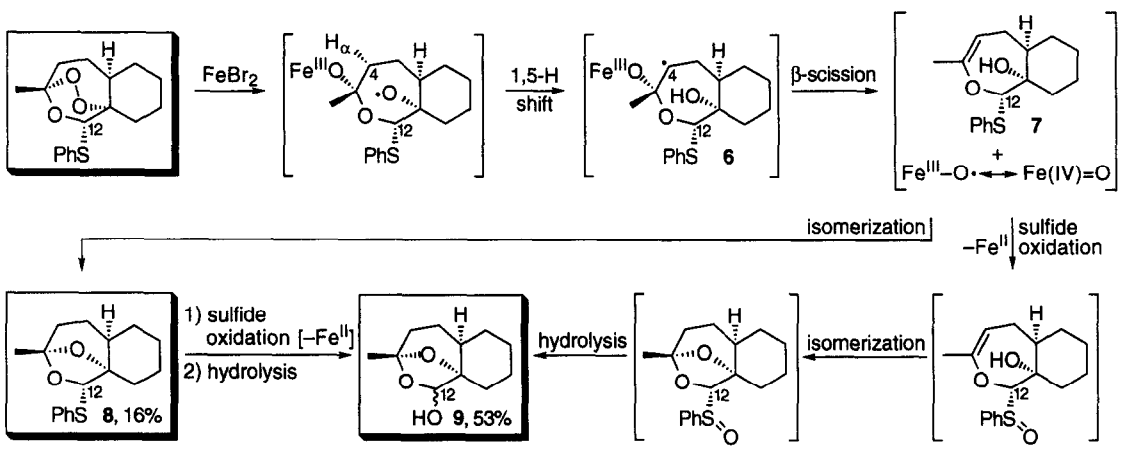
Following our previously described mechanistic studies[9] involving iron(II)-induced degradation of such trioxanes to mimic the biological triggering of artemisinin by heme,[9a] we exposed several of these new sulfide and sulfone trioxanes to ferrous bromide (Scheme II). For the pair of anomeric phenyl sulfides, the formation of lactol **9** or of a 1,5-diketone depended on the sulfide stereochemistry: the 12α-sulfide gave substantial amounts of lactol **9** but no diketone, whereas the 12β-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 12α-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 C_4-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 ether sulfide **8** might then be followed by sulfide → sulfoxide oxidation by the high-valent iron-oxo species still residing close to the α-face of the organic molecule (note that 12β-oriented sulfide trioxane does not form any lactol product). Finally, ferrous ion-promoted hydrolysis of the C_{12}- sulfinyl monothioacetal functional group[11,12] then could reasonably form the observed lactol **9**, isolated as a single diastereomer (C_{12}-stereochemistry not reliably assigned). Whatever the exact sequence of these reactions actually is, this tentative mechanistic proposal is consistent with the 12α-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 12α-**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 12α-**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.



12α	n = 0	19%	16%	53%	0%
12β	n = 0	40%	20%	0%	40%
12β	n = 2	60%	0%	0%	12%

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.

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7. All new compounds were characterized spectroscopically and by combustion analysis or by high resolution mass spectrometry.

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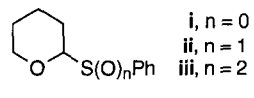
12. As a model system, monothioacetal **i** and its corresponding sulfoxide **ii** and sulfone **iii** were prepared. Their relative rates of ferrous bromide-promoted hydrolysis in aqueous THF are **ii** >> **i** ≈ **iii**. Virtually no hydrolysis of sulfoxide **ii** occurred at r.t. for 1 h, however, in the **absence** of $FeBr_2$.



i, n = 0
ii, n = 1
iii, n = 2