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Synthesis and antimalarial activity of new 1,2,4,5-tetroxanes and novel alkoxy-substituted 1,2,4,5-tetroxanes derived from primary *gem*-dihydroperoxides

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ABSTRACT

A convenient synthesis of new unsymmetrically substituted 1,2,4,5-tetroxanes and novel unsymmetrical alkoxy-substituted 1,2,4,5-tetroxanes starting from primary dihydroperoxides was developed. The structure of some tetroxanes was unambiguously assigned by X-ray crystal analysis giving interesting insights in the configuration and conformation of disubstituted 1,2,4,5-tetroxanes. Some of these tetroxanes showed notable antimalarial activity in vitro.

1. Introduction

In the last two decades cyclic peroxides have attracted the attention of chemists and biologists due to their potent activity against malaria.[1–5] This has stimulated the development of methods for the synthesis of these compounds. Nowadays, cyclic compounds, such as tetroxanes, ozonides, and trioxanes, are considered as the most promising synthetic peroxides in the antimalarial field. 1,2,4,5-Tetroxanes were found to have a high activity as well as a high stability.[6] Some of these compounds exhibit impressive antimalarial activity,[7,8] comparable to or higher than that of the widely used natural peroxide *artemisinin* consisting of a relatively complex tetracyclic endoperoxide skeleton. These findings showed that it is not necessary to simulate the complex *artemisinin* framework to secure superior antimalarial potency but simpler cyclic peroxide structures can be sufficient for a high activity.

The most common methods of synthesis of symmetrical tetroxanes are acid-catalyzed cyclocondensations of hydrogen peroxide with ketones or benzaldehydes[2,5,9,10]; the trimethylsilyl trifluoromethanesulfonate (TMSOTf)-catalyzed cyclocondensation of di-(trimethylsilyl)peroxide with carbonyl compounds,[3,11] the ozonolysis of olefins,[10,12] enol ethers,[13] or *O*-alkyl oximes[14]; the BF_3-catalyzed rearrangement of dioxetanes[15]; and the rearrangement of ozonides in the presence of catalytic amounts of $SbCl_5$ or $ClSO_3H$.[16]

Methods for the preparation of unsymmetrical tetroxanes have attracted more attention, because they provide access to a larger structural variety and thus allow more flexible design of antimalarial drug candidates. Known syntheses of such tetroxanes are based on the cyclocondensation of ketones or aldehydes with steroid[5,17] or alicyclic *gem*-dihydroperoxides (in the presence of sulfuric acid as catalyst[18]), with aliphatic or alicyclic *gem*-dihydroperoxides (in the presence of the $MeReO_3$–HBF_4-system[4] or HBF_4[7] in fluorinated alcohols, or Re_2O_7),[19] the reaction of ketones with *gem*-di(trimethylsilyldioxy)alkanes (TMSOTf[3] as the catalyst), and the BF_3-catalyzed reaction of acetals with alicyclic *gem*-dihydroperoxides.[20]

Alkoxy-substituted 1,2,4,5-tetroxanes are rare. Griesbaum and co-worker[21] and Kuczkowski and co-workers[22] reported the formation of the symmetrical 3,6-dimethoxy-1,2,4,5-tetroxane **2** as the side product of the ozonolysis of *cis*-1,2-dimethoxyethene (*cis*-**1**). Diastereomeric dimethoxytetroxanes **2** were obtained in 5–25% yield (Scheme 1).

Very recently, we described a simple, efficient, and versatile synthesis of primary *gem*-dihydroperoxides (*gem*-DHP) directly from the corresponding aldehydes and hydrogen peroxide.[23] In the present study, we report the synthesis and antimalarial activity of new 1,2,4,5-tetroxanes and novel unsymmetrically monoalkoxy-substituted 1,2,4,5-tetroxanes starting from those primary *gem*-dihydroperoxides.

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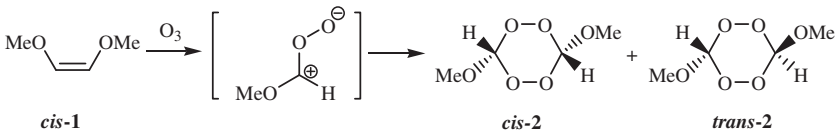
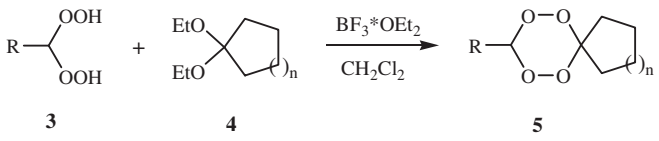


Scheme 1. Formation of 3,6-dialkoxysubstituted 1,2,4,5-tetroxanes by ozonolysis of 1,2-dimethoxyethene.



Scheme 2. Reaction of cyclic acetals **4** with *gem*-DHP **3**.

2. Results and discussion

We started our investigations by reactions of primary *gem*-DHP **3** with cyclic acetals **4**. The reaction conditions were adopted from the previously described procedure,[20] using 0.3 equiv catalyst and 1 h reaction time. Surprisingly, inseparable mixtures of 1-hydroperoxy-1′-alkoxyperoxides rather than the expected 1,2,4,5-tetroxanes were obtained under these conditions. Terent'ev et al. observed similar products in iodine catalyzed reactions.[24] Finally we succeeded in finding conditions for the synthesis of anticipated 1,2,4,5-tetroxanes **5** from primary *gem*-dihydroperoxides **3** and cyclic acetals **4** in moderate yields (Scheme 2, Table 1). These results were achieved by addition of 1 equiv DHP **3** in dichloromethane at rt to 2 equiv of acetal **4** in the same solvent. After 2 min of vigorous stirring 1.4 equiv of BF_3–etherate were added, the reaction was completed after 16 h and the 1,2,4,5-tetroxanes **5** were isolated and purified by column chromatography.

The new compounds **5** were characterized by comparison of significant ^{13}C NMR signals with data reported in the literature for similar compounds.[20] Determination of configuration at the ring positions of the 1,2,4,5-tetroxanes by NMR-techniques is not trivial. The tendency for positioning larger substituents in equatorial positions is not as pronounced[25] and ring inversion has comparatively high barriers.[26] Fortunately, the structure of **5c** was unambiguously determined by X-ray crystal analysis (Fig. 1) revealing the equatorial position of the propyl group attached to the 1,2,4,5-tetroxane ring.

Table 1
Tetroxanes **5** from *gem*-DHP **3** and cyclic acetals **4**

Entry	DHP	R	Acetal	*n*	Tetroxanes **5**/yield (%)	^{13}C NMR:R-*CH*/C_q[a] (ppm)
1	**3a**	Et	**4a**	1	**5a**/43%	109.0/120.2
2	**3a**	Et	**4b**	2	**5b**/33%	109.1/108.7
3	**3b**	*n*-Pr	**4a**	1	**5c**/36%	108.4/120.3
4	**3b**	*n*-Pr	**4b**	2	**5d**/50%	108.4/108.8
5	**3c**	*i*-Pr	**4a**	1	**5e**/15%	111.2/120.2
6	**3c**	*i*-Pr	**4b**	2	**5f**/40%	111.4/108.7

[a] Solvent: $CDCl_3$; measured at 25 °C.

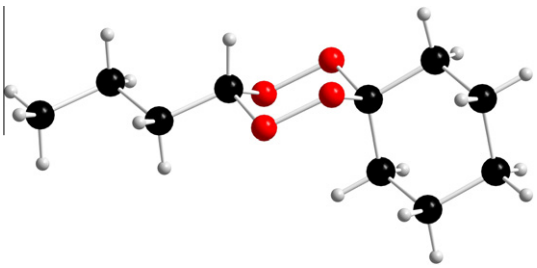


Figure 1. Crystal structure of **5c**.[27]

According to known unsymmetrical 1,2,4,5-tetroxanes which were shown to have antimalarial activity against *Plasmodium falciparum*[3] we tried to introduce further substituents in the tetroxane ring by employing corresponding starting acetals **6**. In this way, benzaldehyde diethyl acetal **6a** and acetophenone dimethyl acetal **6b** gave rise to the formation of 1,2,4,5-tetroxanes **7a–c** and **7d–f**, respectively (Scheme 3, Table 2).

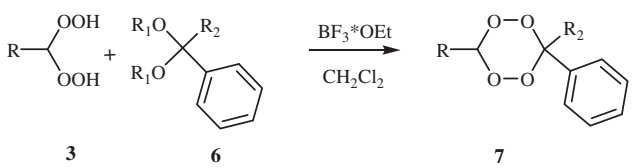
In principle *cis*–*trans* isomers of tetroxanes **7** could be formed in the reaction. We observed only one set of signals in the NMR-spectra. ^1H NMR signals appeared at similar chemical shifts as reported for related tetroxanes.[20] X-ray crystal analysis of **7f** (Fig. 2) gave unambiguous proof for the equatorial positions of the isopropyl and the phenyl substituent placing the methyl group in axial position. Similar configuration was found by X-ray crystal analysis of tetroxane **7a** (see Supplementary data) and can also be expected for the other phenyl-1,2,4,5-tetroxanes **7**.

Unsymmetrically alkoxy-substituted tetroxanes were hitherto unknown. We tried to assign our procedure successfully applied in the preparation of unsymmetrical tetroxanes **7** for the synthesis of alkoxy-substituted 1,2,4,5-tetroxanes using orthoformates **8** instead of acetals. In this way we achieved the synthesis of novel alkoxy-substituted tetroxanes **9** (Scheme 4, Table 3).

The yields obtained for **9e**, **9f**, **9j**, and **9l** are rather low. In cases of 1,2,4,5-tetroxanes with aromatic substituents large quantities of phenol or 2-naphthol were formed. We assume that for these aryl-substituted DHP **3** the Lewis acid (BF_3) causes a Hock-like rearrangement as main reaction leading to the observed hydroxyarenes (Scheme 5).

Tetroxanes **9** were obtained as mixtures of diastereomers *cis*-**9** and *trans*-**9**. The *trans*-isomer was the main product in all cases as detected by NMR, while the *cis*-isomer was only found in traces, if at all. Only this *trans*-tetroxane **9** was separated and isolated by column chromatography except for **9i**. Almost all of the synthesized tetroxanes **9** were obtained as oils. However, tetroxane **9k** is a solid. This allowed for performing an X-ray crystallography analysis of the compound. The measurements confirmed the expected structure, and showed that the isolated tetroxane has a *trans* configuration with both substituents in equatorial positions (Fig. 3). In contrast, the known symmetric dimethoxytetroxane **2** was found to have the *trans* configuration with both methoxy substituents in axial positions to maximize the anomeric effects.[21]

We also synthesized monoalkoxysubstituted tetroxanes **11** from cyclohexanone-derived DHP **10** (Scheme 6, Table 4).



Scheme 3. Reaction of *gem*-DHP **3** with arylsubstituted acetals **6**.

Table 2
Tetroxanes **7a–f** from acetals **6** and *gem*-DHP **3a–c**

Entry	DHP **3**	R	Acetal **6**	R_1	R_2	Tetroxanes **7**/yield (%)	IC_{50} *P. falciparum* K1[a] (μg/mL)
1	**3a**	Et	**6a**	Et	H	**7a**/88	0.277
2	**3b**	*n*-Pr	**6a**	Et	H	**7b**/72	0.397
3	**3c**	*i*-Pr	**6a**	Et	H	**7c**/72	0.324
4	**3a**	Et	**6b**	Me	Me	**7d**/57	1.682
5	**3b**	*n*-Pr	**6b**	Me	Me	**7e**/54	0.475
6	**3c**	*i*-Pr	**6b**	Me	Me	**7f**/60	14.352

[a] The samples were tested in the laboratory of Microbiology, Parasitology, and Hygiene, Antwerp University, campus Groenenborger, Groenenborgerlaan 171, B-2020 Anwerp-Wilrijk, Belgium, reference: chloroquine 0.76.

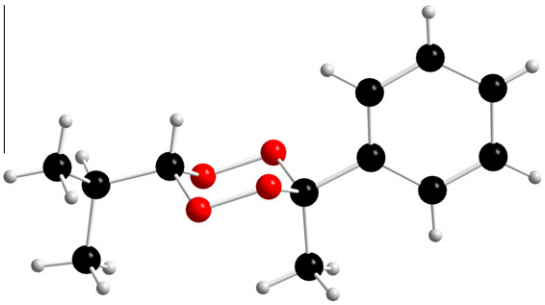
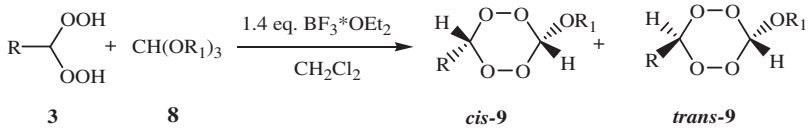


Figure 2. X-ray crystal analysis of tetroxane **7f**.[27]

In some syntheses of alkoxy-substituted tetroxanes **9** (especially with aromatic substituents) and **11** a dramatic decrease of yields was observed at longer reaction times due to decomposition of the corresponding tetroxanes. Reaction times between 5 and 15 min proved effective for a good conversion without too much decomposition.

Antimalarial activities against *P. falciparum* K1 of the tetroxanes synthesized have been examined. Tetroxanes **7a–e** exhibit significant antimalarial activity in vitro with the best IC_{50} value of 0.277 μg/mL for **7a**. In contrast, none of the other tetroxanes showed notable antimalarial activity. These results indicate that relatively minor changes in the structure of the tetroxanes have a profound effect to the antimalarial activities.

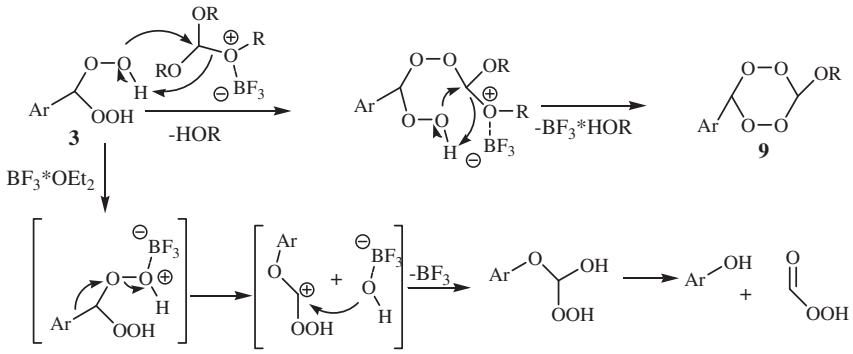


Scheme 4. Reaction of *gem*-DHP **3** with orthoester **8**.

Table 3
Alkoxytetroxanes **9** from orthoesters **8** and *gem*-DHP **3**

Entry	DHP **3**	R	*Ortho*-ester **8**	R_1	*trans*-Tetroxanes **9**/yield (%)
1	**3a**	Et	**8a**	Me	**9a**/24
2	**3b**	*n*-Pr	**8a**	Me	**9b**/26
3	**3c**	*i*-Pr	**8a**	Me	**9c**/32
4	**3d**	*t*-Bu	**8a**	Me	**9d**/20
5	**3e**	Ph	**8a**	Me	**9e**/17
6	**3h**	2-Naphthyl	**8a**	Me	**9f**/5[a]
7	**3a**	Et	**8b**	Et	**9g**/47
8	**3b**	*n*-Pr	**8b**	Et	**9h**/49
9	**3c**	*i*-Pr	**8b**	Et	**9i**/59
10	**3d**	*t*-Bu	**8b**	Et	**9j**/9
11	**3e**	Ph	**8b**	Et	**9k**/55[a]
12	**3h**	2-Naphthyl	**8b**	Et	**9l**/3[a]

[a] Reaction conditions: 0.3 equiv of BF_3*OEt_2, 10 min.



Scheme 5. Proposed mechanism for the competing formation of phenols in the reaction of *gem*-dihydroperoxides **3** with orthoformates.

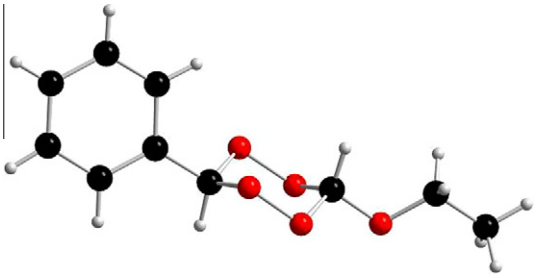
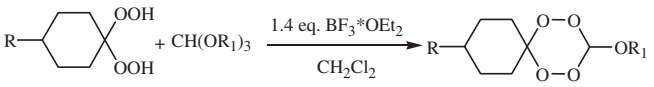


Figure 3. X-ray structure of tetroxane **9k**.[27]



10 **8** **11**

Scheme 6. Reaction of cyclohexanone-derived DHP with orthoesters.

Table 4
3-Alkoxytetroxanes **11** from orthoesters **8** and cyclic *gem*-DHP **10**

Entry	DHP **10**	R	*Ortho*-formate **8**	R_1	Tetroxanes **11**/yield[a] (%)
1	**10a**	H	**8a**	Me	**11a**/12
2	**10b**	H	**8b**	Et	**11b**/32
3	**10c**	*t*-Bu	**8a**	Me	**11c**/16
4	**10d**	*t*-Bu	**8b**	Et	**11d**/32

[a] Reaction conditions: 1.4 equiv of BF_3*OEt_2, 10 min.

In summary, we have developed a convenient approach to new unsymmetric 1,2,4,5-tetroxanes starting from primary geminal dihydroperoxides. For the first time, hitherto unknown unsymmetrical alkoxy-substituted 1,2,4,5-tetroxanes were obtained. Despite the use of quite high amounts of boron trifluoride etherate, most tetroxanes are comparingly stable under these reaction conditions. The configuration of some tetroxanes was unambiguously assigned by X-ray crystal analysis giving interesting insights in the configuration and conformation of disubstituted 1,2,4,5-tetroxanes. Some of the tetroxanes show notable antimalarial activity in vitro.

3. General procedure

To a stirred solution of 2.0 equiv (5.0 mmol) acetal or orthoester in 20 mL of dichloromethane 1.0 equiv (2.5 mmol) of dihydroperoxide in 10 mL of dichloromethane was added. After 2 min 1.4 equiv (443 μL, 3.5 mmol) BF_3*OEt_2 was added quickly under vigorous stirring. After the reaction was complete (TLC) a solution of 1.00 g potassium carbonate in 10 mL of water was added and the mixture was stirred vigorously for another hour. The phases were separated and the aqueous layer extracted three times with 20 mL of dichloromethane. The combined organic layers were dried (sodium sulfate), the solvent evaporated and the crude product separated by column chromatography.

3.1. 3-Ethyl-1,2,4,5-tetraoxaspiro[5.5]undecane 5b

Yellow oil (153 mg, 33%), R_f = 0.65 (petroleum ether/Et_2O = 20:1).

^{1}H NMR ($CDCl_3$): δ [ppm] = 5.72 (t, 1H, J = 5.4 Hz), 2.25 (m, 2H), 1.40–1.63 (m, 10H), 0.97 (t, 3H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$): δ [ppm] = 109.1, 108.7, 31.9, 29.9, 25.4, 23.2, 22.2, 21.8, 7.8.

3.2. 3-Methoxy-6-propyl-1,2,4,5-tetroxane 9b

Yellow oil (109 mg, 26%), R_f = 0.4 (petroleum ether/Et_2O = 98:2).

^{1}H NMR ($CDCl_3$): δ [ppm] = 6.12 (s, 1H), 5.61 (t, J = 5.3 Hz, 1H), 3.63 (s, 3H), 1.45–1.57 (m, 4H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ [ppm] = 115.7, 106.7, 56.1, 29.7, 17.3, 13.7.

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Supplementary data

Supplementary data (experimental details, X-ray crystal analysis of **7a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.151.

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27. Protocoll for obtaining X-ray crystal analyses can be found in Supplementary Data. Supplementary crystallographic data can be obtained free of charge from The Cambride Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data under CCDC 790 407 for **5c**, CCDC 790 408 for **7a**, CCDC 790 409 for **7f**, CCDC 790 410 for **9k**.