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Synthesis, Crystal Structure and Anti-Malarial Activity of Novel Spiro-1,2,4,5-Tetraoxacycloalkanes

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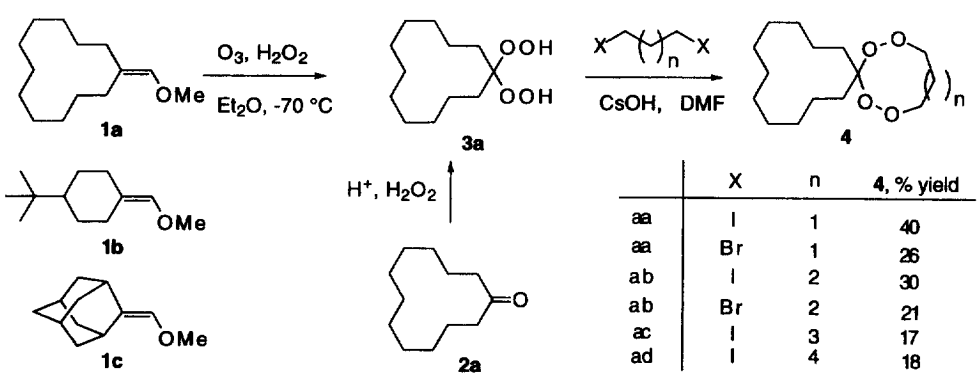
Abstract: (Cycloalkylidene)bishydroperoxides **3** react with 1,n-dihaloalkanes (n = 3-6) in the presence of CsOH-H_2O in DMF affording the corresponding spiro-1,2,4,5-tetraoxacycloalkanes **4** in moderate yields. Compound **4ba** exhibits significant antimalarial activity *in vitro* against *P. falciparum*.

The discovery of pharmacologically active six- and seven-membered cyclic peroxides has stimulated the development of new synthetic routes to such compounds.[1] Since dispiro-1,2,4,5-tetroxanes, often prepared by the acid-catalyzed peroxidation of cycloalkanones,[2] exhibit remarkable anti-malarial activity *in vitro* and *in vivo*,[3] it was anticipated that other cyclic peroxide systems having two geminal peroxide units within the same ring might also be active. In this respect, we now report that treatment of (alkylidene)bishydroperoxides **3** with 1,n-dihaloalkanes in the presence of CsOH in DMF[4] offers a promising procedure for the synthesis of novel spiro-1,2,4,5-tetraoxacycloalkanes **4**.

Ozonolysis of a solution of vinyl ether **1a** and anhydrous hydrogen peroxide (*ca.* 2 equiv.) in diethyl ether at -70 °C [5] gave the corresponding bishydroperoxide **3a** in 33% yield after purification by column chromatography on silica gel (Scheme 1).[6,7] By analogy, bishydroperoxides **3b** and **3c** were



	X	n	4, % yield
aa	I	1	40
aa	Br	1	26
ab	I	2	30
ab	Br	2	21
ac	I	3	17
ad	I	4	18

Scheme 1

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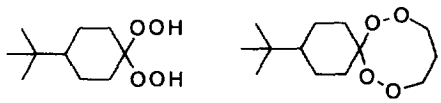
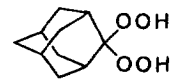
obtained from **1b** and **1c** respectively in 47%, and 42% yield. Bishydroperoxide **3a** could also be readily prepared by treatment of cyclododecanone and hydrogen peroxide in formic acid (*ca.* 50%).[8,9]

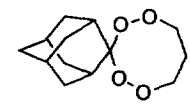


3b (47%)

4ba (26%)



3c (42%)



4ca (19%)

Cycloalkylation of the bishydroperoxides **3a-c** was subsequently attempted using 1,n-dihaloalkanes in the presence of caesium hydroxide monohydrate in DMF. Thus, treatment of a mixture of **3a** and 1,3-diiodopropane (1.5 equiv.) with CsOH-H_2O (2 equiv.) in DMF for 15 h followed by column chromatography (silica gel, eluting with Et_2O/hexane 1:20) afforded initially the novel 1,2,4,5-tetroxocane derivative **4aa** (40% yield) (Scheme 1).[10] Cyclododecanone (45%) was also isolated from a second chromatography fraction. In the absence of the alkylating agent, bishydroperoxide **3a** was found to decompose readily in the presence of CsOH-H_2O in DMF yielding cyclododecanone quantitatively. The other related spiro-peroxides **4ab-ad** were prepared by analogous procedures.

The molecular structures of the crystalline peroxides **4aa** and **4ab**, as depicted in Figures 1 and 2, were unambiguously determined by X-ray crystallographic analysis.[11] The O–O and C–O bond distances in both structures lie within expected ranges suggesting that molecules **4aa** and **4ab** are relatively strain-free. In each case, the twelve-membered cyclododecanylidene ring adopts a square [3333] conformation similar to that observed previously in the structure of the bishydroperoxide **3a**.[12] Interestingly, the eight- and nine-membered peroxide rings in **4aa** and **4ab** favour distorted twist-boat-chair conformations in which the O–O bonds are oriented in a similar manner to those in **3a**. Such an arrangement in **3a** could facilitate the formation of the observed eight- and nine-membered rings.

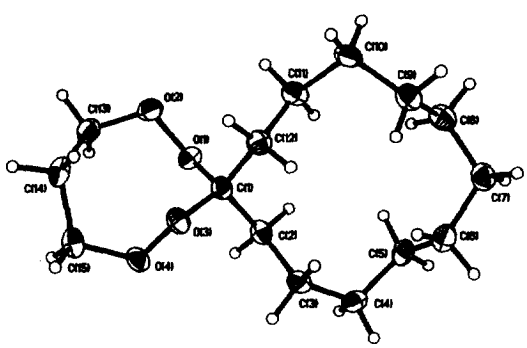


Figure 1. The molecular structure of compound **4aa**.

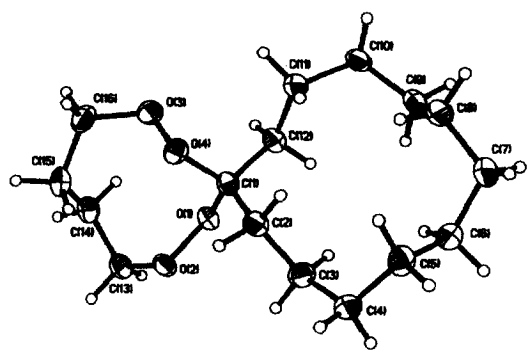


Figure 2. The molecular structure of compound **4ab**.

From the limited results obtained thus far, the efficiency of the cycloalkylation appears to depend on the nature of the halogeno-substituent and the chain length of 1,n-dihaloalkane. In the synthesis of compounds **4aa** and **4ab**, product yields are better with diiodoalkanes rather than the corresponding dibromo homologues. Although the 1,n-diiodoalkanes (n = 1-4) could be used in the cycloalkylation of

bishydroperoxide **3a** thereby providing the corresponding medium-sized 1,2,4,5-tetraoxacycloalkanes **4aa-4ad**, similar reactions of **3a** with 1,2-diiodoethane resulted in the quantitative decomposition to cyclododecanone (Scheme 1).

From the reactions of **3b**,**c** and 1,3-diiodopropane, the corresponding 1,2,4,5-tetroxocane derivatives **4ba** and **4ca** were obtained in moderate yield, 26% and 19%, respectively.

A preliminary study of the antimalarial activities of the derived spiro-peroxides against *P. falciparum*[13] showed that the EC_{50} value of 3-*tert*-butyl-7,8,12,13-tetraoxaspiro[5.7]tridecane **4ba** is as low as 3.0×10^{-9} M (EC_{50} value for artemisinin is 7.8×10^{-9} M), suggesting that this type of spiro-peroxide with two geminal peroxide groups could have considerable promise as a new class of antimalarial agent. Related *in vivo* studies are currently in progress.

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(6) The preparation of bishydroperoxides by the ozonolysis of an alkene in the presence of hydrogen peroxide has been reported once previously: Robertson, J. C.; Verzine, W. J. *J. Org. Chem.* **1970**, *35*, 545.

(7) Ozonolysis of methoxymethylenecyclododecane (**1a**) is representative. An ethereal solution (2.5 M) of anhydrous H_2O_2 was prepared by extraction of 30% aqueous H_2O_2 solution with diethyl ether. The ether extracts were dried over anhydrous $MgSO_4$ and standardized iodometrically. To the

solution of H_2O_2 in ether (25 mL), a vinyl ether **1a** (630 mg, 3.0 mmol) was added and then, a slow stream of ozone (1 equiv.; flow for 15 min) was passed at -70 °C. After adding ether (70 mL), the organic layer was washed with ice-cold potassium dihydrogen phosphate, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, bishydroperoxide **3a** (232 mg, 33%) was isolated from the resulting residue by column chromatography [silica gel, eluting with ether-hexane (1:10) followed by with ether-hexane (3:7)].

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(9) Because bishydroperoxides **3** are potentially hazardous compounds, they must be handled with due care. No particular difficulties have been experienced in the isolation of the bishydroperoxides **3** and in the preparation of the new peroxides **4** using the reaction scales and procedures described.

(10) The synthesis of **4aa** is representative. To a stirred solution of a bishydroperoxide **3a** (348 mg, 1.50 mmol) and $CsOH.H_2O$ (504 mg, 3 mmol) in DMF (25 mL), was added 1,3-diiodopropane (666 mg, 2.25 mmol) by a syringe over 10 min and the mixture was stirred at rt for 16 h. Then, the mixture was poured into ether (70 mL) and the organic layer was washed with ice-cold $NaHCO_3$, saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, 1,2,6,7-tetraoxaspiro[7.11]nonadecane **4aa** (164 mg, 40%) was isolated from the crude product residue by column chromatography [silica gel, eluting with ether-hexane (1:49)] as a crystalline solid: mp 83-84 °C (from hexane); ^{1}H NMR (270 MHz) δ 1.3-1.7 (m, 22 H), 2.1-2.2 (m, 2 H), 4.12 (dt, *J* = 12.5 and 5.6 Hz, 2 H), 4.31 (dt, *J* = 12.5 and 4.7 Hz, 2 H); ^{13}C (67.8 MHz) NMR δ 19.36, 21.90, 22.17, 25.91, 26.07, 26.25, 30.40, 73.94, 112.13. Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.14; H, 10.36. Found: C, 65.91; H, 10.42.
1,2,7,8-Tetraoxaspiro[8.11]icosane **4ab**: mp 97-98 °C (from hexane); ^{1}H NMR (270 MHz) δ 1.3-1.7 (m, 24 H), 2.2-2.3 (m, 2 H), 3.66 (t, *J* = 12.2 Hz, 2 H), 4.26 (dd, *J* = 12.2 and 3.9 Hz, 2 H); ^{13}C NMR (67.8 MHz) δ 19.30, 21.89, 22.17, 25.95, 26.11, 26.43, 30.93, 32.51, 73.85, 111.82. Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.66; H, 10.49.

(11) X-ray diffraction data were collected on a Siemens P4 diffractometer at 160 K using graphite monochromated Mo-K_α λ = 0.71073 Å. The structure was solved by direct methods and refined using least-squares techniques.[14]
Crystal data for **4aa**: $C_{15}H_{28}O_4$, M = 272.37, colourless plate, triclinic, P$\bar{1}$ (No. 2), ***a*** 8.2640 (10), ***b*** 9.266 (2), ***c*** 10.768 (2) Å, α 102.390 (10) β 103.860 (10) γ 103.720 (10) °, U 744.8 (2) Å^3, Z = 2, D_c 1.215 g cm^{-3}, F(000) 300, μ(Mo-K_α) 0.086 mm^{-1}. Final discrepancy factors: R = 0.050 and wR^2 = 0.095.
Crystal data for **4ab**: $C_{16}H_{30}O_4$, M = 286.40, colourless block, triclinic, P$\bar{1}$ (No. 2), ***a*** 10.1486 (9), ***b*** 12.092 (3), ***c*** 14.3437 (18) Å, α 102.212 (11) β 110.689 (9) γ 90.108 (9) °, U 1603.8 (4) Å^3, Z = 4, D_c 1.186 g cm^{-3}, F(000) 632, μ(Mo-K_α) 0.083 mm^{-1}. Final discrepancy factors: R = 0.042 and wR^2 = 0.104.

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