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Synthesis of Novel Hydroperoxy-Substituted 1,2,4,5-Tetroxepanes and 1,2,4,5-Tetroxocanes

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Abstract: Ozonolysis of vinyl ether **1** in the presence of unsaturated hydroperoxides **3** gave the corresponding unsaturated hydroperoxy peracetals **4**, which in turn reacted with ozone in acetic acid to give the novel hydroperoxy-substituted cyclic peroxides containing two peroxide groups in the ring. The structure of 1-methyl-4-phenyl-2,3,5,6-tetroxocanyl hydroperoxide **12** was unambiguously determined by the X-ray analysis.

Recent interest in the antimalarial compound artemisinin and other peroxidic analogues has focused on probing the molecular mechanism of their drug action.[1] Structure-activity studies, considered to play an important part in such investigations, are substantially enhanced by the availability of versatile synthetic methods which permit considerable structural variation.[2] For example, electrophilic cyclization[3] or ozonolysis[4] of unsaturated hydroperoxy acetals provide convenient methods for the synthesis of functionalized 1,2,4-trioxane and its homologues. Since 1,2,4,5-tetroxanes[5,6] and 1,2,4,5,7-pentoxocanes[5] have been shown to exhibit remarkable anti-malarial activity, alternative synthetic routes to cyclic peroxides systems having two peroxide groups in the ring have been investigated. In this respect, we now report that the ozonolysis of unsaturated hydroperoxy peracetals in acetic acid offers a promising procedure for the synthesis of novel hydroperoxy-substituted 1,2,4,5-tetroxepanes and 1,2,4,5-tetroxocanes.

Ozonolysis of a 1:3 mixture of the vinyl ether **1a** and allylic hydroperoxide **3a** in CH_2Cl_2 at -78 °C gave the required peracetal **4a**[7] in 49% yield as outlined in Scheme 1. In a similar manner, the hydroperoxides **4b-d** were obtained in 21-79% yields from the appropriate vinyl ether and allylic hydroperoxide. Subsequent treatment of the unsaturated hydroperoxide **4a** with ozone in diethyl ether did not give the expected tetroxepane **7a** but instead provided the keto hydroperoxide **8a** in 51% yield (Scheme 2). When the same reaction was repeated in acetic acid-CH_2Cl_2 (2:3) at -78 °C, however, the tetroxepane **7a** was isolated in 49% yield (a 1:1 mixture of two stereoisomers).[8] This notable diversion of the reaction pathway is attributed to solvation of the carbonyl oxide moiety in the intermediate **6a** by the acidic solvent, thereby enhancing the electrophilicity of the carbonyl oxide carbon (Scheme 2).[4] Treatment of **7a** with 1 equiv. of

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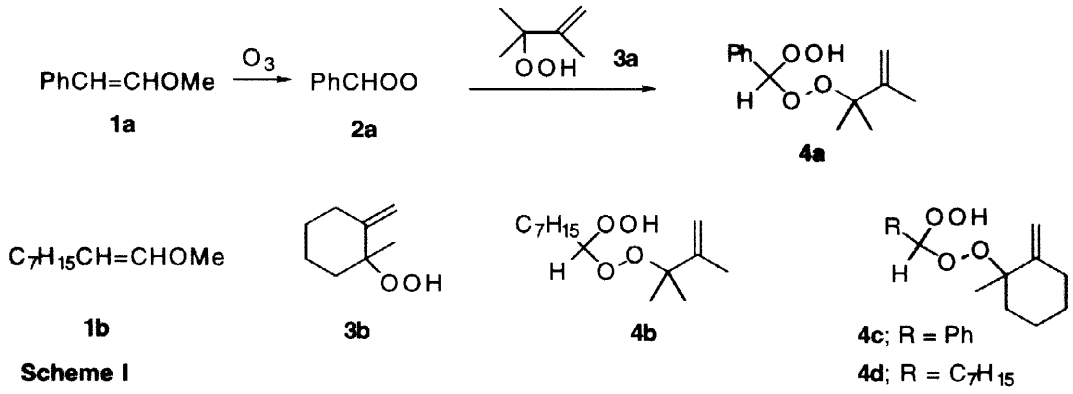
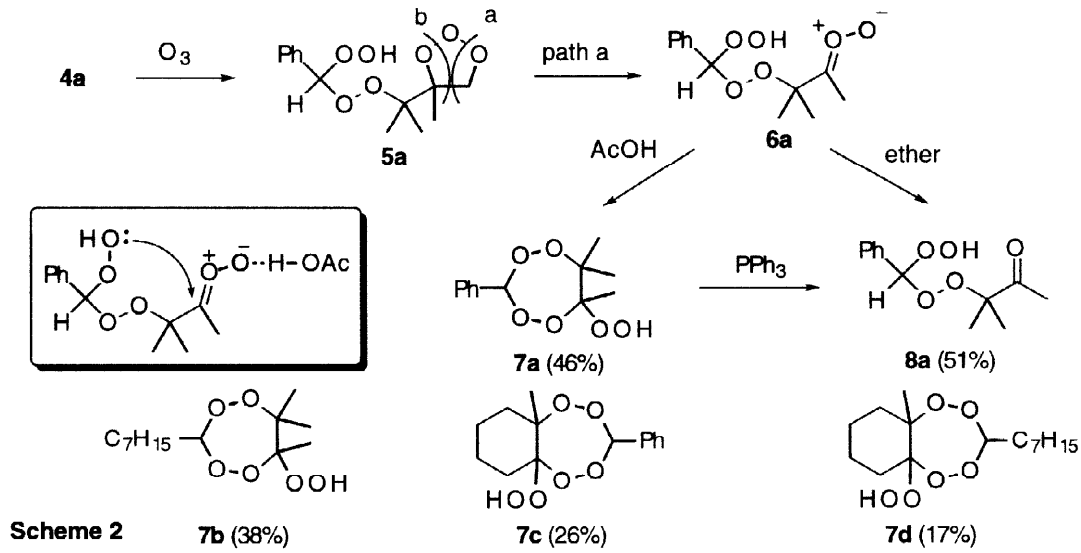


Scheme I

triphenylphosphine in benzene gave **8a** almost quantitatively. From the hydroperoxides **4b-d**, the corresponding tetroxepanes **7b-d** were obtained in yields of 17-38% .

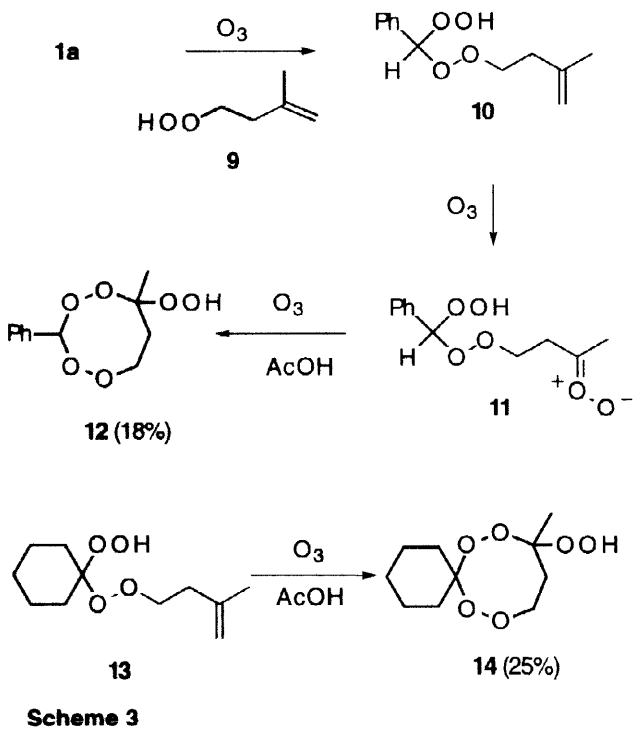


Scheme 2

A more challenging objective was the synthesis of the entropically disfavoured, and hitherto, unknown 8-membered cyclic peroxide system (1,2,4,5-tetroxocane). The required unsaturated hydroperoxide **10**,[3b,9] prepared in 24% yield by the ozonolysis of a vinyl ether **1a** in the presence of the hydroperoxide **9** (3 equiv.) in CH_2Cl_2, was treated with ozone in acetic acid-CH_2Cl_2 affording the desired tetroxocane **12** (18%),[10] together with unidentified oligomeric peroxides (Scheme 3). From the hydroperoxide **13**, the *spiro*-tetroxocane **14** was isolated in 25% yield.

Inconsistent with the expected structure of **12**, no NOE was observed between the methyl and adjacent methylene groups. The structure of **12**, as determined by X-ray crystallographic analysis, is depicted in Figure 1. The central tetroxocane ring in **12** adopts a boat-chair conformation with the phenyl and hydroperoxy groups being *cis*-related. In this arrangement, the hydrogen atoms of the C(3) methylene and C(5) methyl groups are directed away from each other resulting in no significant NOE.

Measurements of the antimalarial activities of the novel cyclic peroxides **7a-d**, **12**, and **14** prepared in this study are in progress.



Scheme 3

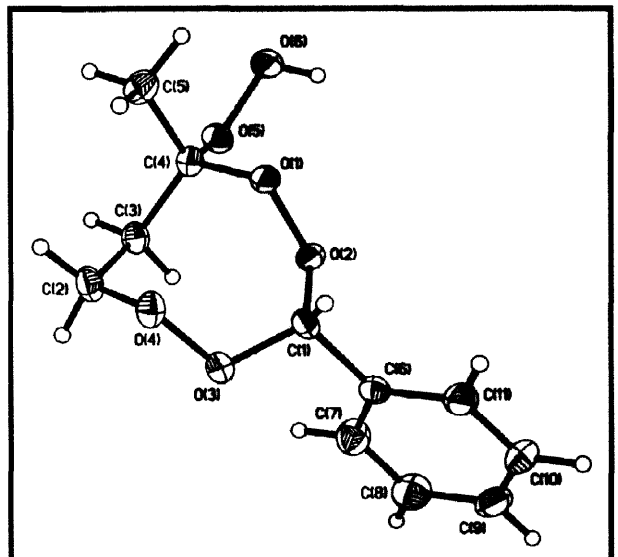


Figure 1. Molecular structure of **12** in the solid state (ORTEP,[12] 50% probability ellipsoids for non-hydrogen atoms; hydrogen atoms are represented by spheres of arbitrary radius.).

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5. Antimalarial activities of 3,6-bis(3-benzoylpropyl)-1,2,4,5-tetroxanes and 1-phenyl-4-(3-benzoyl-propyl)-2,3,5,6,11-penta-oxabicylco[5.3.1]dodecane against *P. falciparum* and cytotoxiciites against FA3a cells were determined. The EC_{50} values were 4.0 x 10^{-7} and 1.3 x 10^{-6} respectively with selectivities of >100 and 24 respectively; Tuchiya, K.; Masuyama, A.; Nojima , M. unpublished results.

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7. **1-(1,1,2-Trimethyl-2-propenylperoxy)benzyl hydroperoxide 4a**: an oil; ^{1}H NMR δ 1.36 (s, 3 H), 1.44 (s, 3 H), 1.88 (s, 3 H), 4.97 (s, 1 H), 5.04 (s, 1 H), 6.32 (s, 1 H), 7.3-7.5 (m, 5 H), 9.04 (s, 1 H); ^{13}C NMR δ 18.71, 23.85, 24.28, 84.89, 108.79, 112.22, 126.95, 128.18, 129.42, 132.96, 148.19. Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.63; H, 7.51

8. **7,7-Dimethyl-5-phenyl-2,3,5-6-tetroxepanyl hydroperoxide 7a** (one isomer): an oil; ^{1}H NMR δ 1.34 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 6.40 (s, 1 H), 7.2-7.4 (m, 5 H), 8.34 (s, 1 H); ^{13}C NMR δ 17.16, 22.18, 24.76, 88.70, 109.83, 114.47, 127.24, 128.61, 130.26, 132.20; NOE measurement confirmed that the phenyl and hydroperoxy groups were *cis*.. Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25; H, 6.25. Found: C, 56.55; H, 6.35. **Another isomer of 7a**: an oil; ^{1}H NMR δ 1.27 (s, 3 H), 1.47 (s, 3 H), 1.56 (s, 3 H), 6.30 (s, 1 H), 7.3-7.5 (m, 5 H), 8.29 (s, 1 H); ^{13}C NMR δ 16.39, 20.72, 23.56, 87.52, 108.16, 113.92, 127.08, 128.46, 129.99, 133.81. Found: C, 56.55; H, 6.07.
7b: an oil; ^{1}H NMR δ 1.33 (s, 3 H), 1.39 (s, 3 H), 1.46 (s, 3 H), 1.2-1.7 (m, 15 H), 5.58 (t, J = 5.6 Hz, 1 H), 8.20 (s, 1 H); ^{13}C NMR δ 14.04, 17.36, 22.25, 22.55, 24.30, 25.00, 28.95, 29.06, 29.18, 31.63, 88.32, 110.73, 114.25. Anal. Calcd for $C_{13}H_{26}O_6$: C, 56.10; H, 9.42. Found: C, 56.55; H, 9.28. **7c**: Mp 91 °C (from ether-hexane); ^{1}H NMR δ 1.53 (s, 3 H), 1.2-2.6 (m, 8 H), 6.44 (s, 1 H), 7.4-7.6 (m, 5 H), 8.10 (s, 1H); ^{13}C NMR δ 19.79, 21.31, 27.85, 35.44, 36.78, 88.81, 110.05, 113.44, 127.21, 128.64, 130.30, 131.97. Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.41; H, 6.39.
7d: an oil; ^{1}H NMR δ 0.88 (t,J = 6.4 Hz, 3 H), 1.3-2.0 (m, 20 H), 1.47 (s, 3 H), 5.64 (t,J = 7.6 Hz, 1 H), 8.21 (s, 1 H); ^{13}C NMR δ 14.05, 19.37, 19.50, 21.39, 22.57, 24.37, 27.53, 28.97, 29.02, 31.63, 35.64, 88.37, 110.98, 113.26.

9. **1-(3-Methyl-3-butenylperoxy)benzyl hydoroperoxide 10**: an oil; ^{1}H NMR δ 1.58 (s, 3 H), 2.43 (t, J = 6.6 Hz, 2 H), 4.30 (t, J = 6.6 Hz, 2 H), 4.81 (s, 1 H), 4.86 (s, 1 H), 6.36 (s, 1 H), 7.2-7.4 (m, 5 H), 9.10 (s, 1 H); ^{13}C NMR δ 22.46, 35.91, 73.55, 108.61, 112.33, 126.92, 127.08, 129.03, 132.10, 142.14.

10. **1-Methyl-4-phenyl-2,3,5,6-tetroxocanyl hydroperoxide 12**: Mp 133-134 °C; ^{1}H NMR δ 1.57 (s, 3 H), 1.7-1.8 (m, 1 H), 3.0-3.1 (m, 1 H), 4.2-4.3 (m, 1 H), 4.5-4.6 (m, 1 H), 6.48 (s, 1 H), 7.3-7.4 (m, 5 H), 8.21 (s, 1 H); ^{13}C NMR δ 17.11, 29.87, 70.62, 108.28, 111.25, 126.94, 128.46, 130.17, 131.29. Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.37; H, 5.60.

11. *Crystal data for* **12**: $C_{11}H_{14}O_6$, M = 242.22 , colourless prism, monoclinic, space group $P2_1/n$ (non-standard setting of No. 14), ***a*** 6.1320 (10), ***b*** 19.993 (3), ***c*** 9.4290 (10) Å, β 96.980 (10) °, U 1147.4 (3) Å^3, Z = 4, D_C 1.402 g cm^{-3}, F(000) 512, μ(Mo-Kα) 0.115 mm^{-1}; final discrepancy indices R1 and wR^2 were 0.039 and 0.113 respectively for 1672 data with I>2σ(I).

12. SHELXTL/PC (Vers 5.03), Sheldrick, G.M. Siemens Analytical X-ray Instruments Inc., Madison, WI, USA.

13. **9-Methyl-7,8,12,13-tetoxaspiro[5,7]tridecan-9-yl hydroperoxide 14**: an oil; ^{1}H NMR δ 1.30 (s, 3 H), 1.4-2.0 (m, 11 H), 3.0-3.1 (m, 1 H), 4.4-4.6 (m, 2 H), 8.24 (s, 1 H); ^{13}C NMR δ 17.90, 22.43, 22.70, 25.30, 30.41, 31.01, 73.03, 108.50, 109.58. Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.28; H, 7.69. Found: C, 51.00; H, 7.80.