

New Synthetic Approaches to 1,2,4,5,7-Pentoxocane Derivatives

Yoshihiro Ushigoe, Masatomo Nojima, and Kevin J. McCullough†

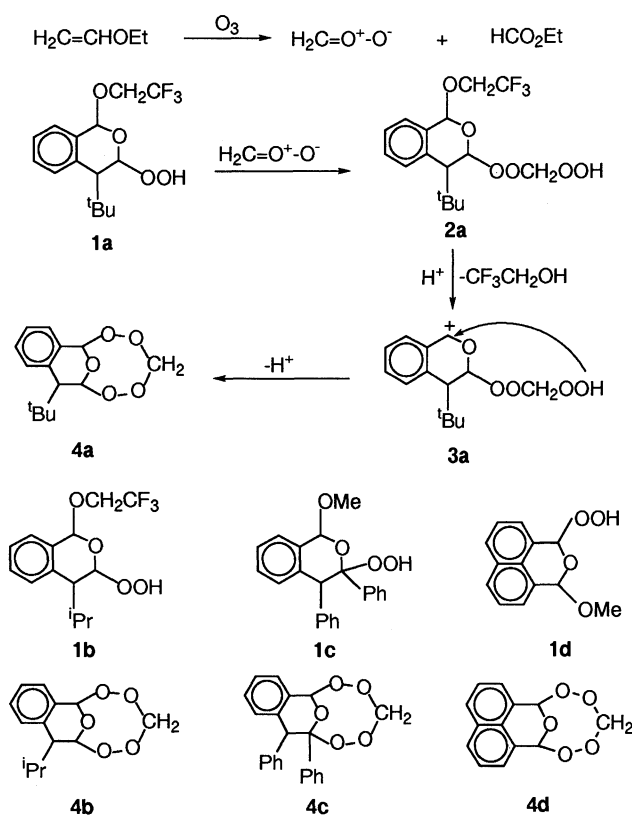
Department of Material Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565

†Department of Chemistry, Heriot-Watt University, Edinburgh, EH14 4AS, Scotland

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Formaldehyde *O*-oxide reacts with α -alkoxy- α' -hydroperoxy ethers to produce the corresponding adducts which can be cyclized under acidic conditions to yield the novel 1,2,4,5,7-pentoxocane derivatives **4a-c** and **8**. The structure of the crystalline 1,2,4,5,7-pentoxocane **8** was determined by X-ray crystallographic analysis.

Mono- and poly-cyclic peroxides have attracted considerable attention as analogues of a number of peroxidic natural products, some of which possess attractive pharmacological properties.^{1,2} In the development of new synthetic approaches to medium-sized cyclic peroxides, α -alkoxy- α' -hydroperoxy ethers, derived from the ozonolysis of cycloalkenes in protic solvents, have been identified as potentially useful precursors.^{3,4} Thus, α -hydroperoxyisochroman derivatives **1a,b** react with formaldehyde *O*-oxide under acidic conditions to produce mixtures of bicyclic 1,2,4,6-tetroxepane and 1,2,4,6,8-pentoxonane derivatives.³ We report herein that capture of the α -alkoxy- α' -hydroperoxy ethers **1** by formaldehyde *O*-oxide followed by intramolecular acid-catalyzed cyclization leads to the formation of the novel 1,2,4,5,7-pentoxocane derivatives **4** (Scheme 1).⁵



Scheme 1.

A solution of the α -hydroperoxyisochroman derivative **1a** (1.8 mmol) and ethyl vinyl ether (5.4 mmol) in methylene chloride was treated with ozone (3.6 mmol) at -70°C . Column chromatography of the crude product mixture on silica gel (elution initially with benzene, followed by elution with diethyl ether-benzene, 3:97) afforded the desired hydroperoxide **2a**^{6,7} (43% yield), together with the unreacted starting material **1a** (41%) (Scheme 1 and Table 1). Similarly, adducts **2b-d** derived from the corresponding α -alkoxy- α' -hydroperoxy ethers **1b-d** were obtained in 15-31% yield (Table 1).

Table 1. Synthesis of 1,2,4,5,7-pentoxocane derivatives

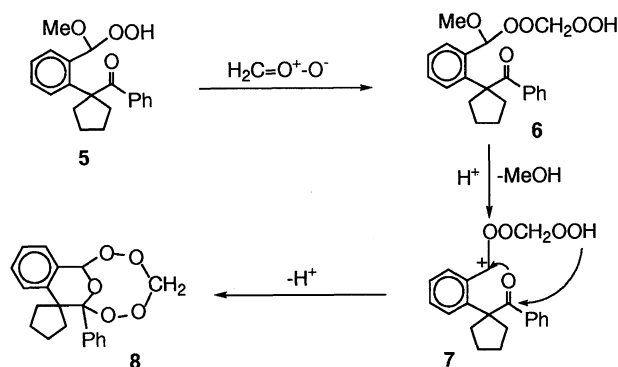
Substr.	Adduct 2 (Yield/%) ^a	Pentoxocane 4 (Yield/%) ^b
1a	2a (43)	4a (33)
1b	2b (31)	4b (44)
1c	2c (15)	4c (20)
1d	2d (25)	4d (22)

^a The yield based on **1**. ^b The yield based on **2**.

Subsequent treatment of the adduct **2a** with trifluoroacetic acid (1 equiv.) in methylene chloride at 20°C for 2 h gave the pentoxocane derivative **4a**⁸ in 33% yield (based on **2a**). Under similar conditions, the pentoxocane derivatives **4b-d** were obtained from the adducts **2b-d** in 21-44% yields (Table 1).

In addition, reaction of the α -alkoxy- ω -oxoalkyl hydroperoxide **5**⁹ with formaldehyde *O*-oxide resulted in the formation of the adduct **6**¹⁰ (73%) which on acid-catalyzed cyclization yields the pentoxocane derivative **8** (19% yield based on **6**).¹¹ X-ray crystallographic analysis of a single crystal of **8** established unambiguously the structure of the novel bicyclic ring system (Figure 1).¹² Although bicyclic peroxides such as **8** normally adopt one conformation in the solid state, atoms O4 and O5 are disordered in a fashion consistent with the population of two conformations (ca. 87: 13).

As outlined in Scheme 2, the acid-catalyzed elimination of



Scheme 2.

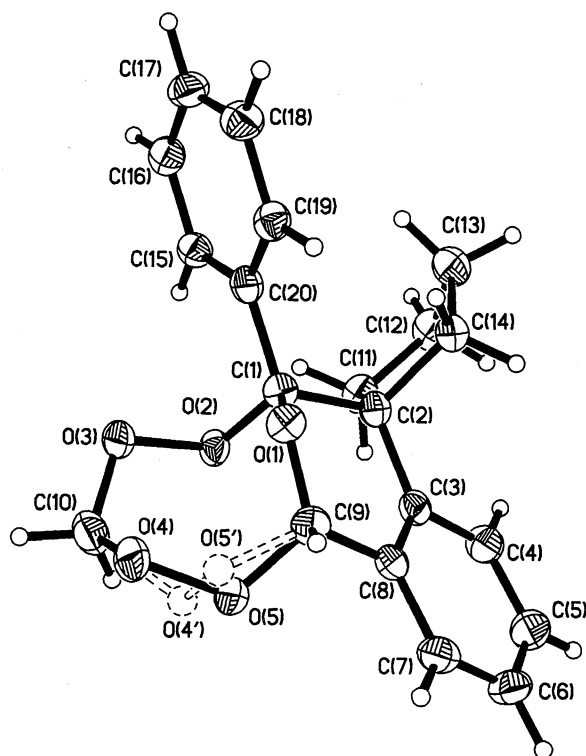


Figure 1. Crystal structure of 1,2,4,5,7-pentoxocane **8** (50% probability ellipsoids).¹³ Positions of the disordered atoms O4' and O5' are indicated as dotted lines.

methanol from **6** may be followed by immediate capture of the carbocationic center by the adjacent carbonyl group to give the pivotal cyclized intermediate **7**.

In conclusion, the novel 1,2,4,5,7-pentoxocane derivatives **4a-d** and **8** are conveniently prepared in two steps from the α -alkoxy- α' -hydroperoxy ethers **1a-d** or the α -alkoxy- ω -oxoalkyl hydroperoxide **5** respectively. Since a variety of solvent-derived products are now available,^{3,4} this methodology should be useful for the synthesis of other eight-membered cyclic peroxides.

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References and Notes

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- 5 The synthetic methods of 1,2,4,5,7-pentoxocane derivatives are quite limited: a) M. Miura, A. Ikegami, M. Nojima, S. Kusabayashi, and K. J. McCullough, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1657. b) M. Miura and M. Nojima, *J. Am. Chem. Soc.*, **102**, 288 (1980).
- 6 Adduct **2a**: oil; ¹H NMR (CCl₄) δ 0.97 (s, 9 H), 2.59 (s, 1H), 4.17 (q, J = 9 Hz, 2 H), 5.17 (br s, 2 H), 5.80 (br s, 2 H), 7.1-7.5 (m, 4 H), 10.07 (s, 1 H).
- 7 Carbonyl oxides are well known to capture alcohols and hydrogen peroxide to give the corresponding adducts.⁴ However, there is no precedent for capture of α -alkoxy- α' -hydroperoxy ethers by carbonyl oxides.
- 8 1,2,4,5,7-Pentoxocane **4a**: mp 83 °C (from ether-hexane); ¹H NMR (CCl₄) δ 1.01 (s, 9 H), 2.53 (s, 1 H), 5.3-5.5 (br s, 2 H), 5.87 (s, 1 H), 6.21 (s, 1 H), 7.2-7.4 (m, 4 H); ¹³C NMR (CDCl₃) δ 28.51, 34.56, 45.87, 96.30, 99.64, 100.67, 126.52, 127.01, 127.94, 128.31, 128.74, 131.68; Mass (CI; isobutane) 267 (M^+ + 1). Anal. Found: C, 63.30; H, 6.86%. Calcd for C₁₉H₁₈O₅: C, 63.15; H, 6.81%. No particular difficulties were experienced in handling any of the new organic peroxides synthesized in this work using the reaction scales and procedures described herein.
- 9 The solvent-derive product **5** was obtained by the ozonolysis of the corresponding indene derivative in methanol: oil; 1.2-2.8 (m, 8 H), 3.40 (s, 3 H), 5.82 (s, 1 H), 6.8-7.7 (m, 9 H), 8.83 (s, 1 H).
- 10 Adduct **6**: oil; ¹H NMR (CCl₄) δ 1.3-2.7 (m, 8 H), 3.35 (s, 3 H), 5.01 (s, 2 H), 6.12 (s, 1 H), 7.0-7.8 (m, 9 H), 10.42 (s, 1 H).
- 11 As the ¹³C NMR spectrum suggests, the 1,2,4,5,7-pentoxocane **8** may exist as a mixture of several conformers in solution: mp 139-140 °C (from methanol); ¹H NMR (CDCl₃) δ 1.2-2.9 (m, 8 H), 5.20 (s, 2 H), 6.49 (s, 1 H), 7.4-8.1 (m, 9 H); ¹³C NMR (CDCl₃) δ 25.57, 28.03, 32.94, 51.29, 97.14, 97.21, 97.38, 99.73, 99.77, 99.85, 100.02, 125.82, 126.11, 126.28, 127.34, 127.68, 127.79, 127.99, 128.18, 128.37, 128.62, 129.34, 144.48; IR 2950, 145, 1320, 1265, 1220, 1105, 1005, 960, 940, 830, 720 cm⁻¹. Anal. Found: C, 70.04; H, 5.78%. Calcd for C₂₀H₂₀O₅: C, 70.58; H, 5.92%.
- 12 **Crystal data.** C₂₀H₂₀O₅, M = 340.36, colorless prisms, triclinic, space group $P\bar{1}$ (No. 2), a = 9.255(2), b = 9.690(2), c = 10.911(2) Å, α = 99.19(3), β = 104.39(3), γ = 114.75(3)°, U = 821.1(3) Å³, Z = 2, D_c = 1.377 g cm⁻³, $F(000)$ = 360, $\mu(\text{Mo-K}\alpha)$ = 0.099 mm⁻¹. The intensity data were collected on an Enraf-Nonius FAST area detector diffractometer using graphite monochromated Mo-K α radiation (λ = 0.710693 Å). Further details of the instrumental settings have been published elsewhere.¹³ The intensity data were corrected for Lorentz and polarization, but not for absorption. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 using anisotropic temperature factors for the non-hydrogen atoms (SHELXTL¹⁴). At convergence, the discrepancy indices R_1 and wR_2 were 0.051 and 0.126 respectively for 1872 data with $F_o > 4\sigma(F_o)$. The final difference Fourier map contained no feature greater than ± 0.36 e Å⁻³.
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