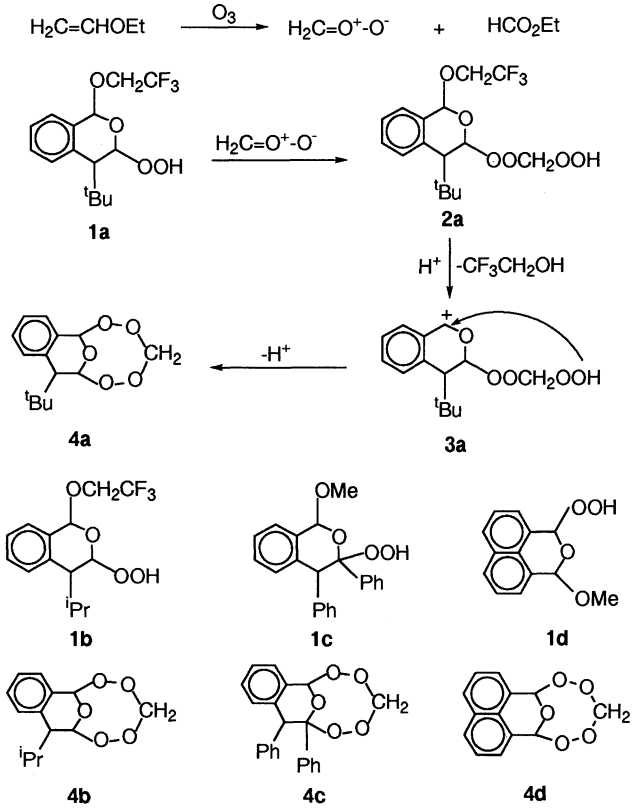
New Synthetic Approaches to 1,2,4,5,7-Pentoxocane Derivatives

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*

(Received May 12, 1995)

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 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

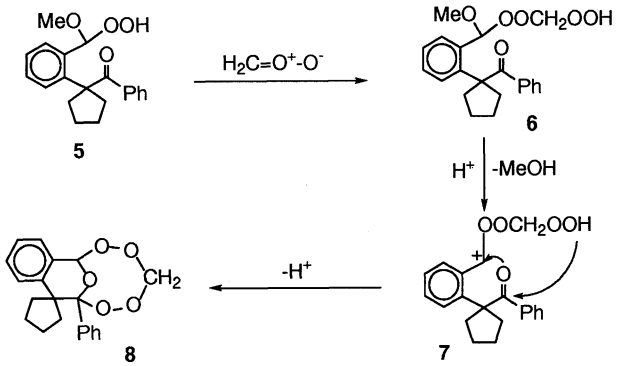
Substr.	Adduct **2** (Yield/ %)[a]	Pentoxocane **4** (Yield/ %)[b]
1a	**2a** (43)	**4a** (33)
1b	**2b** (31)	**4b** (44)
1c	**2c** (15)	**4c** (20)
1d	**2d** (25)	**4d** (22)

[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.

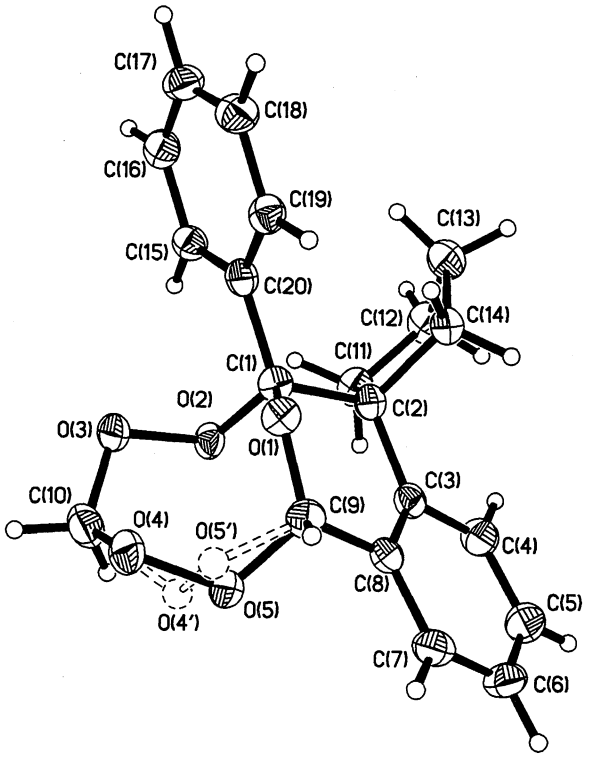


Figure 1. Crystal structure of 1,2,4,5,7-pentoxocane **8** (50% probability ellipsoids).[13] Positions of the disordered atoms O4' and O5' are indicated as dotted lines.

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.

We thank British Council (Tokyo) for the award of travel grants to M. N. and K. J. M. and Professor M. B. Hursthouse (University of Cardiff) for access to data collection facilities through the EPSRC X-ray Service.

References and Notes

1 D. A. Casteel, *Natural Product Reports*, **9**, 290 (1992).
2 I. Saito and S. S. Nittala, "The Chemistry of Perodxides," ed.by S. Patai, Wiley, New York (1983), Chap. 11.
3 Y. Ushigoe, S. Tanaka, M. Nojima, and K. J. McCullough, *Tetrahedron Lett.*, **35**, 9741 (1994).
4 a) K. J. McCullough and M. Nojima, "Organic Peroxides," ed. by W. Ando, New York (1992), Chap. 13. b) P. S. Bailey, "Ozonation in Organic Chemistry," Academic Press, New York (1978).
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; ^{1}H NMR (CCl_4) 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); ^{1}H NMR (CCl_4) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{19}H_{18}O_5$: 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; ^{1}H NMR (CCl_4) 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 ^{13}C 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); ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{20}H_{20}O_5$: C, 70.58; H, 5.92%.
12 *Crystal data.* C_{20} H_{20} O_5 , M = 340.36 , colorless prisms, triclinic, space group PĪ (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) Å^3, Z = 2, D_c = 1.377 g cm^{-3}, F(000) = 360, μ(Mo-K_α) = 0.099 mm^{-1}.
The intensity data were collected on an Enref-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 (SHELXTL[14]). 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}.
13 M. B. Hursthouse, A. I. Karaulov, M. Ciechanowicz-Rutkowska, A. Kolasa and W. Zankowska-Jasinska, *Acta Cryst.*, **C48**, 1257 (1992).
14 G. M. Sheldrick, SHELXTL, University of Göttingen, Germany (1994).