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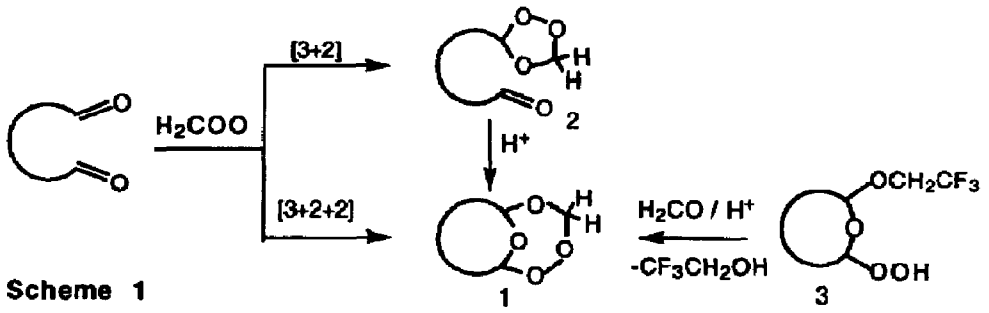
Transformation of Solvent-Derived Ozonolysis Products to Bicyclic Peroxides: Isolation and Characterisation of Novel Pentoxonane Derivatives

Yoshihiro Ushigoe, Shogo Tanaka, Masatomo Nojima
Department of Chemical Process Engineering, Osaka University, Suita, Osaka 565, Japan
Kevin J. McCullough
Department of Chemistry, Heriot-Watt University, Edinburgh, EH14 4AS, Scotland

Abstract: α-Hydroperoxyisochroman derivatives **5** react with formaldehyde under acidic conditions to produce mixtures of bicyclic 1,2,4,6-tetroxepane **9** and 1,2,4,6,8-pentoxonane **10** derivatives. The structure of the compound **10a** was unambiguously established by the X-ray analysis. With acetaldehyde, only the corresponding 1,2,4,6-tetroxepanes **9** were obtained.

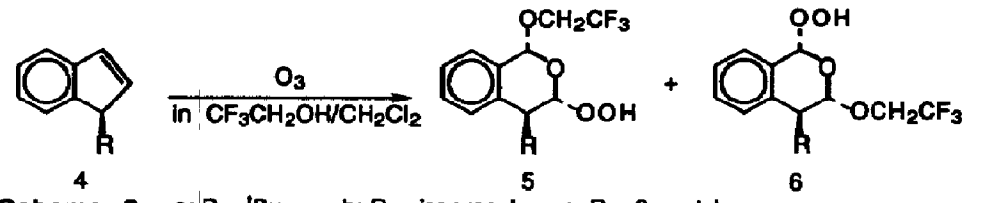
The chemistry of mono- and polycyclic peroxides has attracted considerable attention since a significant number of peroxidic natural products with interesting properties have been isolated.[1,2] Reactions between formaldehyde *O*-oxide and 1,5-keto-aldehydes have recently been reported to produce, via stepwise [3 + 2 + 2] cycloaddition processes, polycyclic adducts **1** which contain the comparatively rare 1,2,4,6-tetroxepane ring system (**Scheme 1**).[3] Moreover, acid-catalysed rearrangement of keto-ozonides **2**, derived from intermolecular [3 + 2] cycloaddition reactions between formaldehyde *O*-oxide and keto-aldehydes, were also found to yield 1,2,4,6-tetroxepane derivatives.



Scheme 1

In the pursuit of alternative synthetic approaches to 1,2,4,6-tetroxepanes **1**, acid-catalyzed cyclization reactions between α-alkoxy α'-hydroperoxy derivatives of cyclic ethers **3** and formaldehyde were investigated (**Scheme 1**).[4] Thus, treatment of 1-*tert*-butylindene **4a** (2 mmol) with ozone (1 equiv) in trifluoroethanol-methylene chloride (15 ml; 1:5, v/v) at 0 °C, followed by column chromatography of the crude reaction mixture on silica gel (eluting initially with benzene followed by diethyl ether-benzene 2:98) afforded the desired solvent-derived product **5a**[5] (55% yield) together with its regioisomer **6a**[6] (31% yield) (**Scheme 2**). Similarly, isochroman derivatives, **5b** (22%) and **5c** (23%) were obtained from the

corresponding indenes **4b,c**. Unlike other more highly substituted indene derivatives, ozonization of the 1-alkylindenes **4** in methanol did not afford readily isolable methoxy isochromans analogous to **5** and **6**.[7]



4 5 6

Scheme 2 a; R = ^{t}Bu b; R = isopropyl c; R = 3-pentyl

Acid catalysed reaction of hydroperoxide **5a** with formaldehyde unexpectedly yielded two crystalline peroxidic products in roughly equal proportions.[8] The first product isolated was readily identified as the 1,2,4,6-tetroxepane derivative **9a**. By X-ray crystallographic analysis, the second product was unambiguously shown to be a novel 1,2,4,6,8-pentoxonane derivative as illustrated in **Figure 1** and structural formula **10a** (**Scheme 3**).[9] Under similar conditions, reactions of hydroperoxides **5b** and **5c** with formaldehyde also gave rise to mixtures of the corresponding tetroxepanes and pentaoxonanes [**9b** (32%) and **10b** (24%) from **5b**, and **9c** (11%) and **10c** (34%) from **5c**].[10] When formaldehyde was replaced by acetaldehyde, hydroperoxides **5a-c** gave the corresponding tetroxepanes **9d-f** respectively as the sole isolable peroxidic products in good yield (60-70%).[11] Analogous reactions between the isomeric hydroperoxide **6** and formaldehyde did not produce cycloadducts because extensive heterolytic cleavage of the peroxidic C–O bond appeared to be the predominant process.

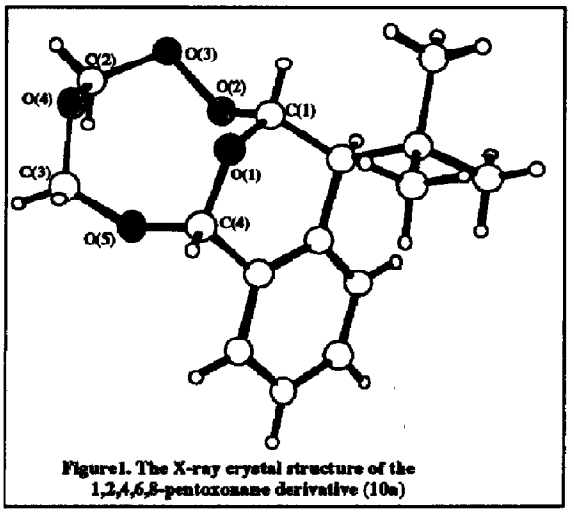
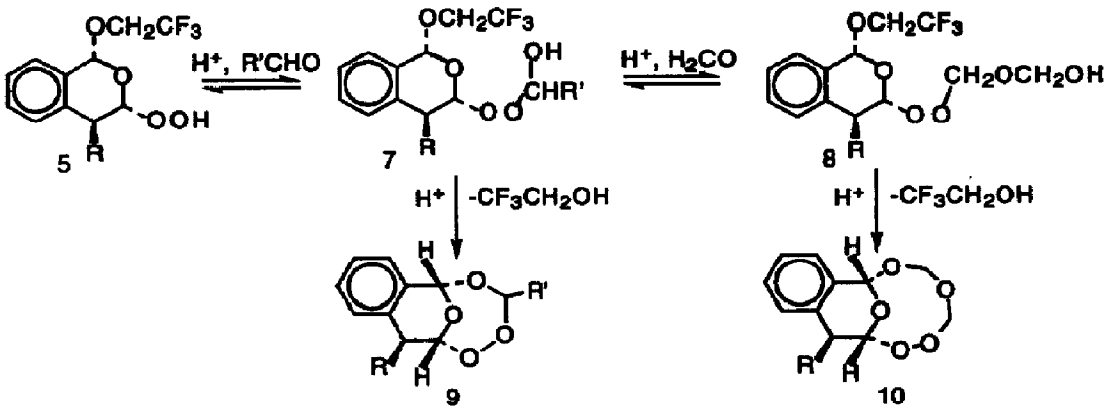


Figure 1. The X-ray crystal structure of the 1,2,4,6,8-pentoxonane derivative (10a)

The formation of the bicyclic peroxides **9** and **10** can be rationalised by the sequence outlined in **Scheme 3**. Protonation of the key intermediate hemiperacetal **7**, resulting from the acid catalysed addition of **5** to the appropriate aldehyde,[4] followed by loss of trifluoroethanol to give a stabilised carbocation and subsequent intramolecular cyclisation via the hydroxy group would produce **9**. Given the propensity of formaldehyde to oligomerise,[12] it is not surprising that the addition of second molecule of formaldehyde to **7** to give **8**, a likely precursor of **10**, could compete effectively under the prevalent acidic conditions with the aforementioned pathway to **9**.

Although recognised as being disfavoured for carbocyclic systems, cyclisation reactions producing 9-membered ring heterocycles are, however, more common, e.g. the formation of hexoxonanes from the peroxidation of ketones.[13] This may be attributed to a comparative reduction in destabilising factors such as Pitzer strain in the intermediates leading to the heterocyclic systems.



Scheme 3

Acknowledgements. We thank British Council (Tokyo) for the award of travel grants to M.N. and K.J.M., and Dr. Alan J. Welch (University of Edinburgh) for access to X-ray data collection facilities.

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3. (a.) Sugimoto, T.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Am. Chem. Soc.*, **1990**, *112*, 3690. (b) McCullough, K. J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 643.
4. 1,2,4-Trioxanes have been prepared by intramolecular oxymercuriation of the hemiperacetals formed from aldehydes and allylic hydroperoxides; see (a) Bloodworth, A. J.; Shah, A. *J. Chem. Soc., Chem. Commun.*, **1991**, 947 and (b) Bloodworth, A. J.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.*, **1992**, 428.
5. All new compounds gave satisfactory elemental analyses.
   Hydroperoxide **5a**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9 H), 2.62 (s, 1 H), 4.26 -4.47 (m, 2H), 5.75 (s, 2 H), 7.0-7.5 (m, 4H), 8.55 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.11, 34.41, 48.65, 65.64 (q, J = 34 Hz), 95.88, 99.74, 123.95 (q, J = 279 Hz), 126.45, 127.14, 128.21, 130.50, 131.80, 131.86; IR 3600-3200, 1280, 1160, 1090, 750 cm^{-1}.
6. Hydroperoxide **6a**: mp 133-134 °C (from benzene); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9 H), 2.71 (s, 1 H), 3.95-4.20 (m, 2H), 5.49 (s, 1 H), 6.10 (s, 1 H), 7.1-7.5 (m, 4 H), 8.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.12, 33.98, 51.33, 64.07 (q, J = 34 Hz), 97.30, 99.13, 124.21 (q, J = 279 Hz), 126.57, 127.00, 128.50, 128.93, 131.29, 133.00; IR 3600-3200, 1280, 1160, 1090, 755 cm^{-1}.
   The molecular structure of **6a** has been established by X-ray crystallographic analysis .
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8. Reaction of hydroperoxide **5a** with formaldehyde (representative procedure): To a solution of **5a** (675 mg, 2.11 mmol) and formaldehyde (0.843 g of 37 wt % aqueous solution) in CH_2Cl_2 (10 ml), was added anhyd. sodium sulfate (500 mg) and the mixture was stirred at 0 °C for 2 h. Then, a solution of trifluoroacetic acid (241 mg, 2.11 mmol) in CH_2Cl_2 (10 ml) was added and the reaction was continued at room temperature for 2 h. After a conventional work-up, the crude product mixture was separated by column chromatography on silica gel (elution with ether-hexane; the ratio was changed from 5:95 to 15:85) to give tetroxepane **9a** (165 mg, 31% yield) and pentoxonane **10a** (160 mg, 27% yield).
Tetroxepane **9a**: mp 48-50 °C; ^{1}H NMR (200 MHz, CCl_4) δ 1.03 (s, 9 H), 2.41 (s, 1 H), 4.76 (d, J = 10 Hz, 1 H), 5.06 (d, J = 10 Hz, 1 H), 5.89 (s, 1 H), 6.12 (s, 1 H), 7.1-7.6 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.57, 34.29, 48.34, 94.56, 95.28, 100.87, 125.87, 126.79, 128.10, 130.91, 131.45, 134.97.
Pentoxonane **10a**: mp 105 °C; ^{1}H NMR (200 MHz, CCl_4) δ 0.97 (s, 9 H), 2.55 (s, 1 H), 4.79 (d, J = 6 Hz, 1 H), 5.02 (s, 2 H), 5.18 (d, J = 6 Hz, 1 H), 5.72 (s, 1 H), 5.98 (s, 1 H), 7.12-7.43 (m, 4 H); molecular weight (vapor pressure osmometer; CH_2Cl_2) 278; MASS (CI; isobutane) 281 ($M^+ + 1$).

9. *Crystal data for* ***10a***. $C_{12}H_{18}O_6$, M = 280.3, colourless prisms, monoclinic, space group $P2_1/n$ (non-standard setting of No. 14), a 6.3115 (14), b 30.689 (9), c 7.536 (3) Å, U 1453.0 (8) Å^3, Z = 4, D_c 1.281 g cm^{-3}, F(000) 600 μ(Mo-K_α) 0.90 cm^{-1}. The intensity data were collected on an Enraf-Nonius CAD4 diffractometer (2θ range: 1.0 – 50.0 °; ω - 2θ scanning; Mo-K_α X-radiation). Final discrepancy factors R and R_w were 0.058 and 0.077 respectively for 1753 intensities with $I > 3\sigma(I)$.

10. Tetroxepane **9b**: mp 47-48 °C (from hexane); ^{1}H NMR (200 MHz, CCl_4) δ 0.96 (d, J = 7 Hz, 3 H), 1.06 (d, J = 7 Hz, 3 H), 1.8-2.3 (m, 1 H), 2.48 (d, J = 6 Hz, 1 H), 4.87 (d, J = 9.5 Hz, 1 H), 5.11 (d, J = 9.5 Hz, 1 H), 5.70 (s, 1 H), 6.07 (s, 1 H), 7.1-7.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 19.98, 20.72, 31.46, 45.48, 94.60, 95.46, 101.14, 125.96, 126.65, 128.55, 129.62, 130.80, 136.13.
Pentoxonane **10b**: oil; ^{1}H NMR (200 MHz, CCl_4) δ 0.86 (d, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 1.7-2.2 (m, 1 H), 2.61 (d, J = 5.5 Hz, 1 H), 4.90 (d, J = 6.5 Hz, 1 H), 5.09 (s, 2 H), 5.15 (d, J = 6.5 Hz, 1 H), 5.51 (s, 1 H), 5.91 (s, 1 H), 7.1-7.4 (m, 4 H); MASS (CI; isobutane) 267 ($M^+ + 1$).
Tetroxepane **9c**: oil; ^{1}H NMR (200 MHz, CCl_4) δ 0.6-1.7 (m, 11 H), 2.74 (d, J = 3.5 Hz, 1 H), 4.85 (d, J = 9 Hz, 1 H), 5.08 (d, J = 9 Hz, 1 H), 5.58 (s, 1 H), 6.02 (s, 1 H), 7.2-7.6 (m, 4 H).
Pentoxonane **10c**: mp 113 °C (from ether-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.6-1.8 (m, 11 H), 2.84 (d, J = 2 Hz, 1 H), 4.88 (d, J = 7 Hz, 1 H), 5.07 (s, 2 H), 5.14 (d, J = 7 Hz, 1 H), 5.39 (s, 1 H), 5.85 (s, 1 H), 7.1-7.5 (m, 4 H).

11. Tetroxepane **9d**: ^{1}H NMR (200 MHz, CCl_4) δ 1.03 (s, 9 H), 1.21 (d, J = 5 Hz, 3 H), 2.38 (s, 1 H), 4.97 (q, J = 5 Hz, 1 H), 5.83 (s, 1 H), 5.99 (s, 1 H), 7.2-7.5 (m, 4 H).
Tetroxepane **9e**: oil; ^{1}H NMR (200 MHz, CCl_4) δ 1.01 (d, J = 6 Hz, 6 H), 1.24 (d, J = 5 Hz, 3 H), 1.8-2.2 (m, 1 H), 2.41 (d, J = 6 Hz, 1 H), 5.04 (q, J = 5 Hz, 1 H), 5.68 (s, 1 H), 5.98 (s, 1 H), 7.1-7.5 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 17.42, 20.14, 20.75, 31.34, 45.58, 93.87, 101.25, 101.55, 125.93, 126.62, 128.28, 128.37, 129.72, 131.51.
Tetroxepane **9f**: mp 69-70 °C (from ether-hexane); ^{1}H NMR (200 MHz, CCl_4) δ 0.7-1.7 (m, 14 H), 2.70 (d, J = 3.5 Hz, 1 H), 5.45 (q, J = 5 Hz, 1 H), 5.61 (s, 1 H), 5.97 (s, 1 H), 7.1-7.5 (m, 4 H).

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