The Synthesis of Novel 3,4-Dihydro-1,2,5,7,4-tetroxazocine Derivatives *via* Extended [3 + 3 + 2] Cycloaddition Reactions between a Carbonyl Oxide, a Nitrone and an Aldehyde

Syuzo Satake,[a] Yoshihiro Ushigoe,[a] Masatomo Nojima*[a] and Kevin J. McCullough*[b]

[a] *The Department of Chemical Process Engineering, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan*

[b] *Department of Chemistry, Heriot-Watt University, Edinburgh, UK EH14 4AS*

Ozonolysis of acenaphthylene in the presence of a nitrone **2** yields the corresponding polycyclic peroxide **5** containing the novel dihydro-1,2,5,7,4-tetroxazocine ring system; the structure of the crystalline adduct **5a** has been unambiguously determined by X-ray crystallographic analysis.

Cyclic peroxides are found to be intrinsic structural features of several potent, physiologically active natural products.[1] As an alternative to conventional oxygenation and peroxidation procedures, ozonolysis reactions have been shown to provide useful synthetic routes to a range of novel cyclic peroxide systems, including those with medium sized rings.[2] Although carbonyl oxides, generated *in situ* as key intermediates from the reaction of ozone with olefins, very often simply react with carbonyl compounds to form ozonides (1,2,4-trioxolanes), they may participate in a variety of cycloaddition reaction types with appropriate co-reactants to afford, *e.g.*, 1,2,4-dioxazolidines from [3 + 2] cycloadditions with imines,[3,4] dihydro-1,2,4,5-trioxazines from [3 + 3] cycloadditions with nitrones,[5] 1,2,4 trioxepines from [3 + 4] cycloadditions with conjugated enones,[6] and bicyclic 1,2,4,6-trioxepane derivatives from stepwise [3 + 2 + 2] cycloaddition reactions with 1,5-keto aldehydes.[7]

We now report the first examples of polycyclic peroxides, containing the novel dihydro-1,2,5,7,4-tetroxazocine system, formally derived from the extended [3 + 3 + 2] cycloaddition reaction between a carbonyl oxide moiety, a nitrone, and an aldehyde group.

Treatment of a solution of acenaphthylene **1** in diethyl ether with ozone led to the exclusive formation of an unidentified polyozonide presumably derived from successive intermolecular [3 + 2] cycloaddition reactions between the carbonyl oxide moieties and the aldehyde groups in the intermediate **3**.[8] On repeating the ozonation of **1** (608 mg, 1 mmol) in the presence of α-phenyl-*N*-benzylnitrone **2a** (844 mg, 4 mmol), however, polyozonide formation was substantially suppressed (240 mg) and a crystalline peroxidic product (571 mg, 40%),† identified by X-ray crytallographic analysis as the polycyclic peroxide **5a** containing the novel dihydro-1,2,5,7,4-tetroxazocine ring system as depicted Fig. 1,‡ together with the acenaphthylene ozonide **6** (71 mg, 10%) were obtained instead (Scheme 1).§

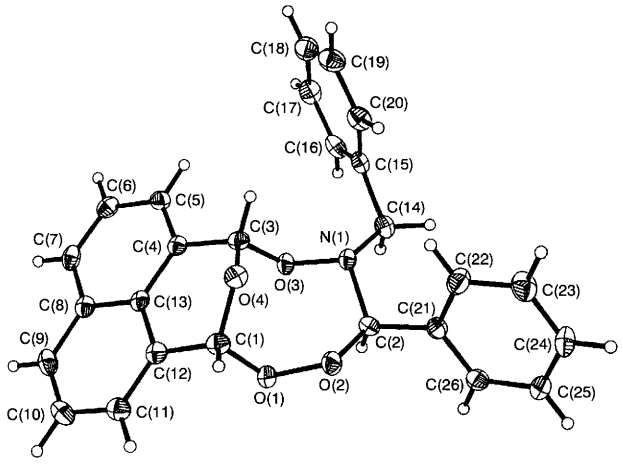
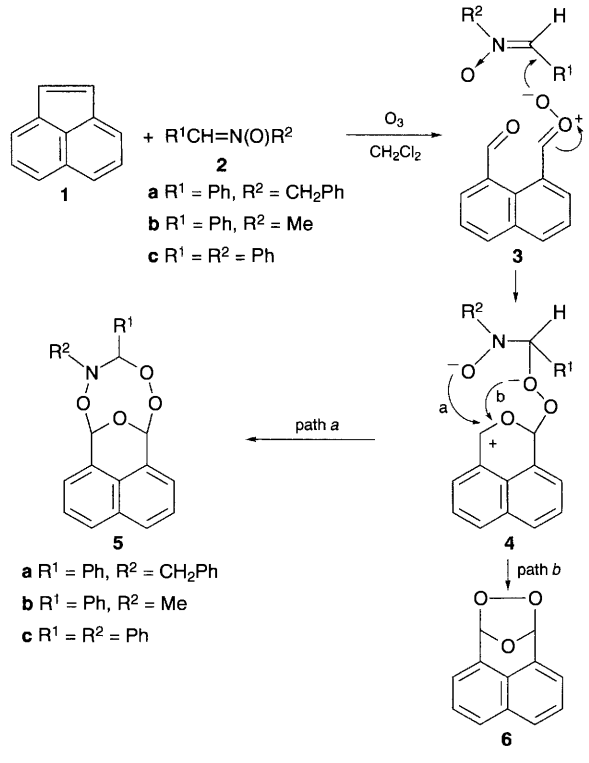


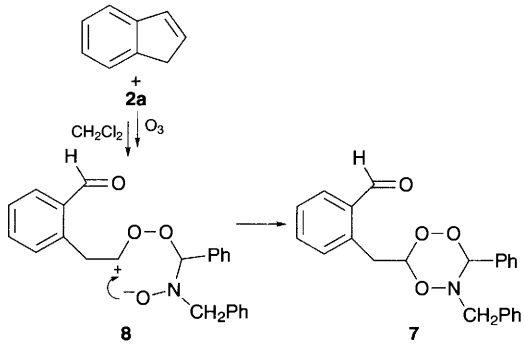
Fig. 1 X-ray crystallographic structure of 3,4-dihydro-1,2,5,7,4-tetroxazocine **5a** (50% probability ellipsoids, SHELXTL[10])

Moreover, from the ozonolyses of acenaphthylene **1** in the presence of the nitrones **2b** and **2c**, the corresponding tetroxazocine derivatives **5b** and **5c** were obtained in yields of 25 and 11% respectively together with ozonide **6**[8] (30% in the case of **2b**, and 45% in the case of **2c**).

The formation of the nitrone-incorporated cyclic peroxides **5** and the novel assistance by the nitrone in the formation of the ozonide **6** can be readily rationalised by the stepwise addition–cyclisation mechanism outlined in Scheme 1. Decomposition of the primary ozonide derived from the cycloaddition of ozone to



Scheme 1



Scheme 2

acenaphthylene would yield the sterically-congested carbonyl oxide intermediate **3**. In the first step of the sequence leading to the cyclic peroxides **5** or ozonide **6**, the terminal oxygen of the carbonyl oxide moiety of **3** most likely attacks the electrophilic carbon of the highly-polar nitrone **2** followed by immediate intramolecular cyclisation involving the adjacent aldehyde group to produce the zwitterionic intermediate **4**. Subsequent intramolecular cyclisation at either the N–O oxygen (path *a*) or the peroxide oxygen (path *b*) affords the tetroxazocine derivative **5** or ozonide **6** respectively.

The involvement of the adjacent aldehyde group in **3** appears to be crucial for the formation of tetroxazocine derivative **5** because ozonolysis of a mixture of indene and a nitrone **2a** provides the dihydrotrioxazine **7** (18%)¶ derived from [3 + 3] cycloaddition of the nitrone with the carbonyl oxide moiety in the more flexible intermediate **8** (Scheme 2).[5]

We thank British Council (Tokyo) for a Collaborative Research Project (CRP) award to K. J. M. and M. N. and Professor M. B. Hursthouse, University of Cardiff for access to data collection facilities through the EPSRC X-ray Crystallographic Service.

Received, 26th April 1995; Com. 5/02662H

Footnotes

† *Selected physical and spectroscopic data* for **5a**: mp 183–185 °C (from ethyl acetate–hexane); ^{1}H NMR δ 3.50 (d, J = 14 Hz, 1 H), 3.74 (d, J = 14 Hz, 1 H), 5.56 (s, 2 H), 6.60 (s, 1 H) and 6.8–8.2 (m, 16 H); ^{13}C NMR δ 59.17, 98.20, 98.68, 100.97, 124.55, 124.90, 124.99, 125.55, 125.69, 25.85, 126.75, 127.55, 128.09, 128.29, 128.57,129.03,129.14, 129.72, 13.17, 130.27, 132.49, 134.10 and 136.94. IR ν/cm^{-1} 2850, 1440, 1260, 1110, 1040 and 840.

For **5b**: mp 130–135 °C (from ethyl acetate–hexane); ^{1}H NMR δ 2.53, (s, 3 H), 5.37 (s, 1 H), 6.47 (s, 1 H), 6.63 (s, 1 H) and 7.1–8.1 (m, 11 H); ^{13}C NMR δ 43.11, 97.02, 98.71, 102.23, 124.53, 124.94, 125.12, 125.55, 125.75, 126.92, 127.31, 128.43, 128.77, 129.25, 129.765, 129.97, 132.53, 133.28, 134.14 and 135.20.

For **5c**: mp 145–150 °C (from ethyl acetate–hexane); ^{1}H NMR δ 5.91 (s, 1 H), 6.49 (s, 1 H), 6.74 (s, 1 H) and 7.0–8.0 (m, 16 H); ^{13}C NMR δ 97.32, 99.01, 101.40, 124.53, 125.30, 125.46, 125.73, 125.80, 125.97, 126.72, 126.86, 128.14, 128.25, 128.79, 129.33, 129.45, 129.94, 132.60, 133.62 and 147.46. Satisfactory elemental analyses were obtained for new peroxides **5a–c**.

‡ *Crystal data* for $C_{26}H_{21}NO_4$, M = 411.44, colourless prisms, triclinic, space group $P\bar{1}$ (No. 2), a = 7.996(2), b = 11.751(2), c = 11.765(2) Å, α = 108.42(3), β = 90.17(3), γ = 107.30(3)°, U = 995.6(3) Å^3, Z = 2, D_c = 1.372 g cm^{-3}, F(000) = 432, μ(Mo-Kα) = 0.093 cm^{-1}.

The intensity data were collected on an Enraf-Nonius FAST area detector diffractometer using graphite monochromated Mo-Kα radiation (λ = 0.710693 Å). Further details of the instrumental settings have been published elsewhere.[9] The intensity data were corrected for Lorentz and polarisation, 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[10]). At convergence, the discrepancy indices R_1 and wR_2 were 0.051 [for 2085 data with $F_o > 4\sigma(F_o)$] and 0.123 (all 2730 unique data) respectively. The final difference Fourier map contained no feature greater than ±0.31 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

§ The byproduct, $(PhCH_2NO)_2$, derived from the ozonolysis of the nitrone **2a**, was also isolated in 43% yield.[5]

¶ *Spectroscopic data* for dihydrotrioxazine **7**: oil; ^{1}H NMR δ 3.3–3.5 (m, 2 H), 3.6–3.9 (m, 2 H), 5.63 (s, 1 H), 5.96 (t, J = 6 Hz, 1 H), 7.1–7.8 (m, 14 H) and 10.11 (s, 1 H); ^{13}C NMR δ 33.37, 56.32, 100.43, 105.41, 127.04, 127.40, 127.96, 128.28, 128.75, 128.82, 128.97, 129.15, 130.71, 132.13, 132.20, 132.47, 133.46, 136.01 and 192.36.

References

1 D. A. Casteel, *Nat. Prod. Rep.*, 1992, **9**, 289.
2 K. J. McCullough and M. Nojima, in *Organic Peroxides*, ed. W. Ando, Wiley, Chichester, 1992, pp. 661–728.
3 M. Mori, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Chem. Soc., Chem. Commun.*, 1988, 1550; K. J. McCullough, M. Mori, T. Tabuchi, H. Yamakoshi, S. Kusabayashi and M. Nojima, *J. Chem. Soc., Perkin Trans. 1*, 1995, 41.
4 M. R. Iesce, F. Cermola, F. Giordano, R. Scarpati and M. L. Graziano, *J. Chem. Soc., Perkin Trans. 1*, 1994, 3295.
5 M. Mori, T. Sugiyama, M. Nojima, S. Kusabayashi and K. J. McCullough, *J. Org. Chem.*, 1992, **57**, 2285.
6 M. Mori, H. Yamakoshi, M. Nojima, S. Kusabayashi, K. J. McCullough, K. Griesbaum, P. Krieger-Beck and I.-C. Jung, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1335.
7 K. J. McCullough, T. Sugimoto, S. Tanaka, S. Kusabayashi and M. Nojima, *J. Chem. Soc., Perkin Trans. 1*, 1994, 643.
8 T. Sugimoto, M. Nojima and S. Kusabayashi, *J. Org. Chem.*, 1990, **55**, 3816.
9 M. B. Hursthouse, A. I. Karaulov, M. Ciechanowicz-Rutkowska, A. Kolasa and W. Zankowska-Jasinska, *Acta Crystl*, 1992, **C48**, 1257.
10 G. M. Sheldrick,SHELXTL, University of Göttingen, Germany, 1994.