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, SHELXTL¹⁰)

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





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

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Footnotes

 \dagger Selected physical and spectroscopic data for 5a: mp 183–185 °C (from ethyl acetate-hexane); ¹H 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 v/cm⁻¹ 2850, 1440, 1260, 1110, 1040 and 840

For 5b: mp 130-135 °C (from ethyl acetate-hexane); ¹H NMR & 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); ¹³C NMR & 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); ¹H 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.

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 $\ddagger Crystal data$ for C₂₆H₂₁NO₄, M = 411.44, colourless prisms, triclinic, space group $P\overline{1}$ (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) Å³, 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-K α 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 F² using anisotropic temperature factors for the non-hydrogen atoms (SHELXTL¹⁰). 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, (PhCH2NO)2, derived from the ozonolysis of the nitrone 2a, was also isolated in 43% yield.5

¶ Spectroscopic data for dihydrotrioxazine 7: oil; ¹H 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); ¹³C NMR & 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.

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