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SINGLET OXYGENATION OF CIS,CIS-1,5-CYCLOOCTADIENE: A CONVENIENT SYNTHETIC ENTRY INTO 5,8-DIFUNCTIONALIZED OXYGEN DERIVATIVES OF 1,3-CYCLOOCTADIENE.[1]

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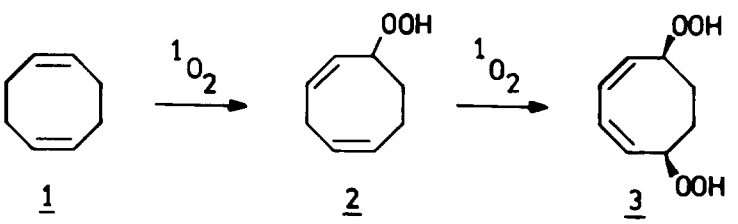
SUMMARY: The 6-hydroperoxy-1,4-cyclooctadiene (2), which is formed in the photosensitized oxygenation of 1,5-cyclooctadiene (1), affords on further singlet oxygenation 5,8-dihydroperoxy-1,3-cyclooctadiene (3), which via triphenylphosphine reduction leads to cis-5,8-dihydroxy-1,3-cyclooctadiene (4) and subsequent pyridinium chlorochromate oxidation to 1,3-cyclooctadien-5,8-dione (5).

Photosensitized singlet oxygenation of 1,5-cyclooctadiene (1) in methanol, using rose bengal as sensitizer, has been reported[3] to afford 6-hydroperoxy-1,4-cyclooctadiene (2), as shown in eq. 1. It appeared to us that the 1,4-cyclooctadiene



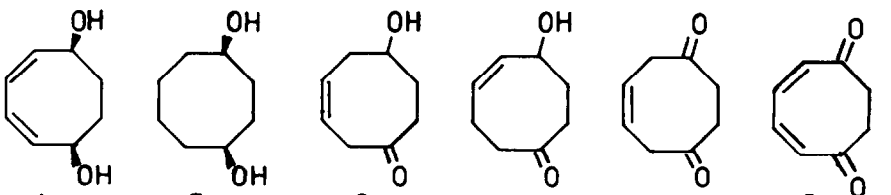
1 2 3 (eq.1)

derivative 2 should be susceptible towards further singlet oxygenation to the dihydroperoxide 3 in view of the fact that 1,4-dienes react readily with singlet oxygen via ene-reaction with the doubly activated methylenic hydrogens.[4] Since the sequence

in eq. 1 constitutes a convenient synthetic entry into 5,8-difunctionalized oxygen derivatives of 1,3-cyclooctadiene, we have investigated the exhaustive singlet oxygenation of 1,5-cyclooctadiene and herein report on the feasibility and synthetic utilization of this approach.

When a CH_2Cl_2 solution of 1,5-cyclooctadiene (25.4 mmol in 50 ml) was submitted to tetraphenylporphyrin (2 mg) sensitized photo-oxygenation at 0°C under the conditions described previously,[5] a mixture of the monohydroperoxide 2 and the dihydroperoxide 3 was formed,[3] as evidenced by ^{1}H-NMR monitoring. On further singlet oxygenation the monohydroperoxide 2 was mostly converted into the dihydroperoxide 3. In a separate experiment it could be confirmed that the authentic monohydroperoxide 2 afforded the dihydroperoxide 3 on TPP photo-sensitized singlet oxygenation in $CDCl_3$ (^{1}H-NMR monitoring) at 0°C. Silica gel chromatography, eluting with 10:1 $CHCl_3$/EtOH, afforded 67% of the dihydroperoxide 3 and 8% monohydroperoxide 2. The dihydroperoxide 3 was isolated as a colorless, crystalline solid, mp 50-55°C, 93% pure by peroxide titration; however, it proved difficult to recrystallize this substance in view of its great hygroscopic nature. The following spectral data support the structure assignment: ^{1}H-NMR ($CDCl_3$/TMS) δ (ppm) 1.9-2.2 (m, 4H), 4.6-5.0 (m, 2H), 5.5-6.2 (m, 4H), and 8.30 (s, 2H); IR ($CHCl_3$) ν(cm^{-1}) at 3550-3300 (OH) 2950 and 2890 (aliphatic Ch), and 1650 (C=C).

Unequivocal structure proof for the dihydroperoxide 3 could be provided via triphenylphosphine reduction in $CHCl_3$, affording the labile 5,8-dihydroxy-1,3-cyclooctadiene (4), 83% yield, mp 87-89°C (from 1:3 acetone/hexane), after silica gel column chromatography, eluting with 10:1 $CHCl_3$/EtOH. The spectral data of the

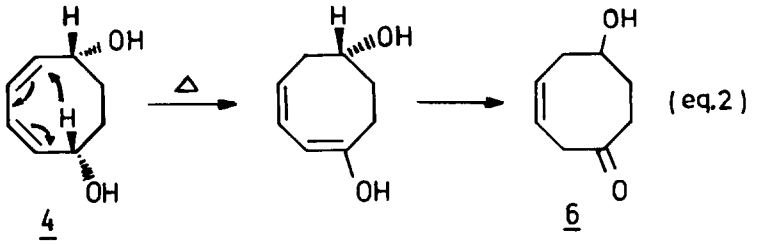


4 5 6 6a 7 8

diol 4 are: ^{1}H-NMR ($CDCl_3$, TMS) δ (ppm) 1.9-2.1 (m, 4H), 2.20 (s, 2H), 4.3-4.7 (m,

2H), and 5.4-5.9 (m, 4H); IR (neat) $\nu(cm^{-1})$ 3500-3300 (OH), 3020 (olefinic C-H), 2950 and 2880 (aliphatic C-H), and 1650 (C=C). On catalytic hydrogenation over Pd/C in CH_3OH, the unsaturated diol 4 was converted quantitatively into the hygroscopic cis-1,4-dihydroxycyclooctane (5), mp 81-83°C from ethyl acetate (lit.[6] mp 83-84°C). Its spectral data are: ^{1}H-NMR ($CDCl_3$, TMS) δ (ppm) 1.5-2.0 (m, 12H), 2.30 (s, 2H), and 3.90 (m, 2H); IR ($CHCl_3$) $\nu(cm^{-1})$ 3700-3350 (OH) and 2940 and 2860 (aliphatic C-H). Not only does the cis-1,4-diol 5 confirm that the dihydroxy functionalities in the 1,3-cyclooctadiene derivative 4 are 5,8-positioned, but that they are in the cis-geometrical arrangement. Therefore, the dihydroperoxy derivative of 1,3-cyclooctadiene 3 must have the oxygen functionalities also in the cis-5,8 arrangement. Inspection of Dreiding models of the hydroperoxide 2 reveals that the ene-reaction should prefer cis-functionalization of the second hydroperoxy group at the 8-position since the corresponding 3-methylenic hydrogen has the best axial allignment for singlet oxygenation.[7]

It is of interest to mention that the cis-5,8-dihydroxy-1,3-cyclooctadiene (4) is thermally quite labile, rearranging slowly into 6-hydroxy-3-cyclooctenone (6) at room temperature. More effectively, on 3h reflux in C_6H_6-ethanol the diol 4 is quantitatively converted into the hydroxyenone 6, colorless oil, whose spectral data are identical to those reported[3] for structure 6a: ^{1}H-NMR (CCl_4, TMS) δ (ppm) 1.5-2.7 (m, 8H), 4.3 (s, 1H), 4.4-4.7 (m, 1H), and 5.5-5.7 (m, 2H); IR (neat) $\nu(cm^{-1})$ 3600-3300 (OH), 3030 (olefinic C-H), 2990-2850 (aliphatic C-H), 1700 (C=O), and 1660 (C=C). Oxidation of hydroxyenone 6 with pyridinium chlorochromate[8] gave the enedione 7 in 50% yield, colorless liquid, bp 120°C (bath temp.) at 3.0 mm, n_D^{20} 1.5056, correct elemental composition for $C_8H_{10}O_2$.[9] The following spectral data confirm its structure: ^{1}H-NMR (CCl_4, TMS) δ (ppm) 2.60 (s, 4H), 3.00-3.20 (m, 4H), and 5.65-5.90 (m, 2H); IR (CCl_4) $\nu(cm^{-1})$ 3020 (olefinic C-H), 2960 and 2920 (aliphatic C-H) and 1705 (C=O). This chemical transformation clearly establishes our claimed hydroxyenone 6 structure. The facile 4→6 thermal rearrangements can be readily rationalized in terms of an allowed 1,5-hydrogen shift, followed by ketonization (eq. 2). Inspection of a Dreiding model of diol 4 shows that its α-hydrogens are most conveniently alligned conformationally for such a 1,5-hydrogen shift.



4 6

Finally, pyridinium chlorochromate oxidation of the diol 4 afforded the dienone 8 in 60-70% yield as a pale yellow oil, whose spectral properties were identical to those reported for the authentic substance.[10] The convenient preparation of this interesting 5,8-diketo-1,3-cyclooctadiene via the synthetic sequence 1→3→4→8 reported here, illustrates the usefulness of the novel difunctionalization of cyclic dienes via sequential ene-reaction with singlet oxygen. We are presently extending the generality and utility of this synthetic concept.

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