

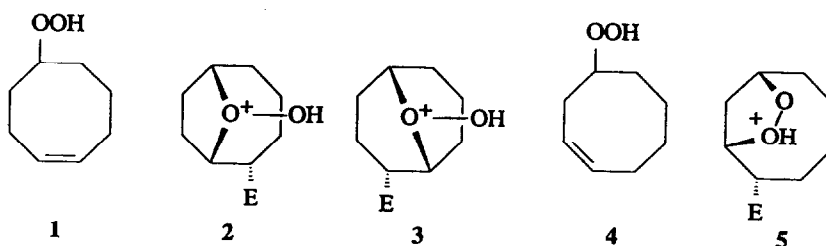
POLAR AND RADICAL BICYCLIZATIONS OF CYCLO-OCT-3-EN-1-YL HYDROPEROXIDE TO AFFORD 2-FUNCTIONALISED-8,9-DIOXABICYCLO[5.2.1]DECANES

A.J. Bloodworth* and Michael D. Spencer

Chemistry Department, University College London,
20 Gordon Street, London WC1H 0AJ (UK).

Summary: 8,9-Dioxabicyclo[5.2.1]decanes with bromomercurio, hydroxy, bromo, iodo, and oxo substituents at the 2-position have been prepared from cyclo-oct-3-en-1-yl hydroperoxide; the reactions include extensions of cycloperoxyiodination and of peroxy radical cyclization to the formation of bicyclic peroxides.

We have shown that cyclo-oct-4-en-1-yl hydroperoxide (1) reacts with suitable electrophiles to afford *gem*-dialkylperoxonium ions (2 and 3) which are a new class of oxygen-transfer reagents.¹ It is believed that the stereochemical constraints of the cyclo-octane ring render intramolecular nucleophilic attack by the non-hydroxylic oxygen upon the initially formed cation preferable to that by the hydroxylic oxygen; the latter would afford isomeric *vic*-dialkylperoxonium ions and thence bicyclic peroxides after deprotonation.



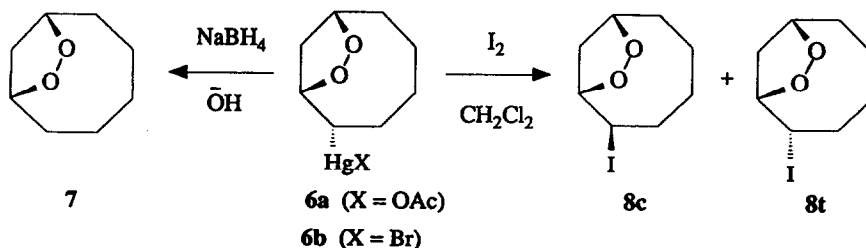
We have recently prepared cyclo-oct-3-en-1-yl hydroperoxide (4) from the corresponding *N*-*p*-tosylhydrazine.² It was anticipated that this isomer, in similar reactions with electrophiles, would yield bicyclic peroxides since formation of *vic*-dialkylperoxonium ions (5) would now be the sterically favoured process. Reactions with sources of positive halogen were therefore expected to extend the recently reported³ cycloperoxyhalogenation process to the synthesis of bicyclic peroxides. Evidence has been presented that iodocyclization with *N*-iodosuccinimide

(NIS) involves a free radical chain rather than a polar mechanism.³ As far as we are aware, there are no reports in the literature of a peroxy radical cyclization that yields a bicyclic peroxide. Thus, the reaction of hydroperoxide (4) with NIS and with more conventional radical initiators⁴ would be of special interest.

We describe here the products obtained from the reactions of cyclo-oct-3-en-1-yl hydroperoxide (4) with mercury(II) acetate, *meta*-chloroperoxybenzoic acid (MCPBA), *N*-bromosuccinimide (NBS), NIS, iodine, and di-*t*-butylperoxyoxalate (DBPO) in the presence of oxygen. These reactions have afforded new 2-functionalised-8,9-dioxabicyclo[5.2.1]decanes and thereby have (i) extended both cycloperoxyhalogenation and peroxy radical cyclization to the preparation of bicyclic peroxides, and (ii) provided indirect support for the aforementioned steric effects in the formation of *gem*-dialkylperoxonium ions from cyclo-oct-4-en-1-yl hydroperoxide.

The reactions (except for that with DBPO/O₂) were each carried out in a deuteriated solvent in a 5 mm NMR tube using *ca.* 50 mg (0.35 mmol) of cyclo-oct-3-en-1-yl hydroperoxide (4) and were monitored by 100 MHz ¹³C NMR spectroscopy. The product distributions are expressed as molar ratios (%) calculated from the peak heights of the CH₂ resonances. The new bicyclic peroxides were isolated by semi-preparative HPLC on 5 μm SiO₂ using 10-25% ethyl acetate in hexane as eluant. Molecular formulae were confirmed by high resolution mass spectrometry, each peroxide giving a molecular ion with a satisfactory accurate mass.

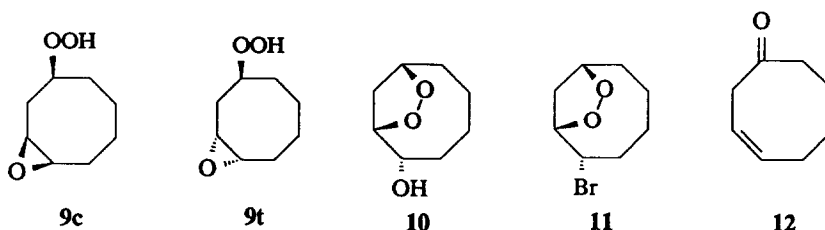
The reaction with mercury(II) acetate in CD₂Cl₂ was markedly accelerated by placing the NMR tube in an ultrasonic cleaning bath. A single isomer of 2-acetoxymercurio-8,9-dioxabicyclo[5.2.1]decane (presumably *trans*; 6a) was the sole product and was isolated as the corresponding organomercury(II) bromide (6b) after anion exchange. Additional proof of structure was provided by reduction to the known⁵ mercury-free peroxide (7) and by iodolysis which yielded a 58:42 mixture of *cis* and *trans* iodides (8c and 8t).



These results support our earlier interpretations of the formation of 2,6- and 2,10-dibromo-8,9-dioxabicyclo[5.2.1]decanes in reactions where the intermediacy of 8- and

2-trifluoroacetoxymercuriocyclo-oct-3-en-1-yl hydroperoxides respectively was suggested.^{5,6}

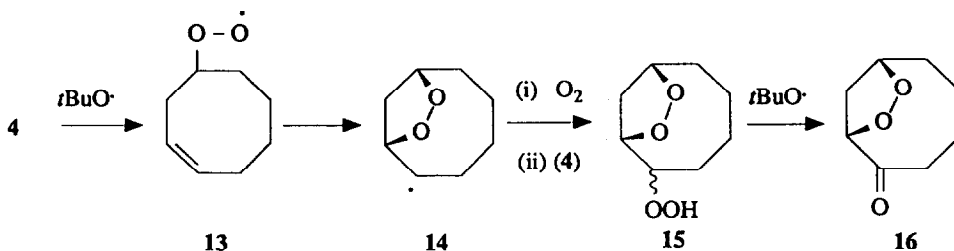
The reaction with MCPBA in CD_2Cl_2 rapidly afforded a 56:44 mixture of *cis* and *trans* epoxyhydroperoxides (**9c** and **9t**). After 4 days the signals for (**9t**) had disappeared to be replaced by those of the bicyclic peroxide (**10**); both (**10**) and (**9c**) were isolated and fully characterised.



Although the reactions with NBS and with NIS in CD_2Cl_2 again afforded single isomers of 2-substituted [5.2.1]-peroxides [**11** (51%) and **8t** (28%) respectively], they differed from the reactions above in that a gas (presumably O_2) was evolved and 49-55% of cyclo-oct-3-en-1-one (**12**) was also obtained. These differences are thought to indicate the incursion of a substantial radical component with these reagents (see later). By changing to a more polar solvent, namely CD_3OD , ketone formation was completely (NBS) or largely (NIS) suppressed and high yields of peroxides **11** (100%) and **8t** (90%) were obtained. Given the stereospecificity of the halogenobicyclizations, it seems probable that they involve polar mechanisms in both solvents since the iododemercuration of **6a** (above), which presumably involves the same intermediate radical (**14**) as would be formed by peroxy radical cyclization, gave both *cis* and *trans* iodides.⁷

The yield of iodide **8t** was also markedly improved by treating the hydroperoxide (**4**) with molecular iodine rather than NIS in CD_2Cl_2 ; 21% of cyclo-oct-3-en-1-ol was also formed, presumably by competing reduction of the hydroperoxide (**4**) by iodide generated in the bicyclization. The absence of ketone (**12**) among the products is consistent with the reaction proceeding by a wholly polar mechanism, as found for related iodocyclizations of acyclic hydroperoxides.³

In the NBS and NIS reactions, the cyclo-oct-3-en-1-one (**12**) is thought to arise by a radical mechanism because it was the major product (60%) when hydroperoxide (**4**) was treated with the *t*-butoxyl radical source DBPO in benzene saturated with oxygen; also formed were cyclo-oct-3-en-1-ol (11%) and 8,9-dioxabicyclo[5.2.1]decan-2-one (**16**) (29%).



The alcohol and ketone (12) could arise by Russell disproportionation⁸ of the peroxy radical (13), but this would give equimolar amounts. Thus, there must be an additional route to ketone (12) and we suggest a radical-initiated carbonyl-forming elimination.⁹ The bicyclic peroxide (16) is thought to arise by a similar elimination in 2-hydroperoxy-8,9-dioxabicyclo[5.2.1]decane (15), itself formed by cyclization of the peroxy radical (13) and trapping of the resultant radical (14) by oxygen. If this mechanism is correct then, to the best of our knowledge, this represents the first peroxy radical cyclization to afford a bicyclic peroxide. Previous radical cyclizations that give bicyclic peroxides have all involved carbon-centred radicals in the bicyclization step.¹⁰

Acknowledgement

We thank the SERC for a Research Studentship (to M.D.S.).

References and Notes

1. A.J. Bloodworth, T. Melvin and J.C. Mitchell, *J. Org. Chem.*, 1986, **51**, 2612; *idem ibid*, 1988, **53**, 1078; S.P. Best, A.J. Bloodworth and M.D. Spencer, *J. Chem. Soc., Chem. Commun.*, 1990, 416.
2. A.J. Bloodworth, J.L. Courtneidge, R.J. Curtis, and M.D. Spencer, *J. Chem. Soc., Perkin Trans. 1*, in the press.
3. A.J. Bloodworth and R.J. Curtis, *J. Chem. Soc., Chem. Commun.*, 1989, 173.
4. A.J. Bloodworth, R.J. Curtis and N. Mistry, *J. Chem. Soc., Chem. Commun.*, 1989, 954, and references therein.
5. A.J. Bloodworth, J.A. Khan and M.E. Loveitt, *J. Chem. Soc., Perkin Trans. 1*, 1981, 621.
6. A.J. Bloodworth and B.P. Leddy, *Tetrahedron Letters*, 1979, 729.
7. It is recognised, however, that abstraction of iodine from NIS³ is likely to be more sterically demanding than that from I₂.
8. G.A. Russell, *J. Am. Chem. Soc.*, 1957, **79**, 3871.
9. J.A. Howard in "The Chemistry of Peroxides", S. Patai (ed.), Wiley, Chichester, 1983, p 250.
10. *Inter alia*: D.E. O'Connor, E.D. Mihelich and M.C. Coleman, *J. Am. Chem. Soc.*, 1981, **103**, 223; *idem ibid*, 1984, **106**, 3577; E.J. Corey, C. Shih, N-Y. Shih and K. Shimoji, *Tetrahedron Letters*, 1984, **25**, 5013; E.J. Corey, K. Shimoji and C. Shih, *J. Am. Chem. Soc.*, 1984, **106**, 6425.