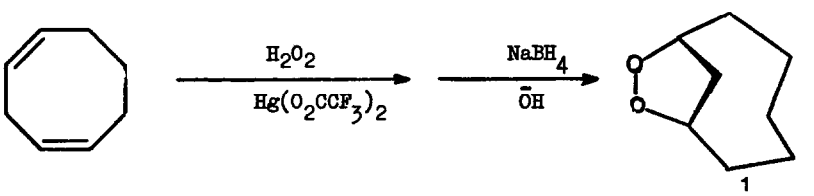
Tetrahedron Letters No. 8, pp 729 - 732. 0040-4039/79/0215-0729$02.00/0

SYNTHESIS OF 8,9-DIOXABICYCLO[5.2.1]DECANE DERIVATIVES FROM CYCLOOCTENE

A.J. Bloodworth* and B.P. Leddy.
Christopher Ingold Laboratories,
Chemistry Department, University College London,
20 Gordon Street,
London WC1H OAJ

Summary. Singlet oxygenation of cyclooctene gives 2-cyclooctenyl hydroperoxide which affords isomeric 2, cis-10-dibromo-8,9-dioxabicyclo[5.2.1]decanes on treatment with mercury(II) trifluoroacetate then bromine, and yields cis-10-bromo-8,9-dioxabicyclo[5.2.1]decane on treatment with bromine then silver trifluoroacetate.

Recently we described the preparation of 8,9-dioxabicyclo[5.2.1]decane (1) by the peroxymercuration and reduction of 1,4-cyclooctadiene.[1]

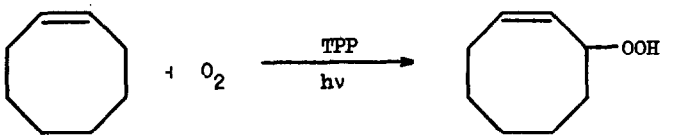


1

This bicyclic peroxide is of interest because it is the first isolated homologue of the 2,3-dioxabicyclo[2.2.1]heptane nucleus of prostaglandin endoperoxides to contain the novel feature of a strain-free 1,2-dioxacyclopentane ring. We now wish to report two new methods for generating the 8,9-dioxabicyclo[5.2.1]decane system that both employ the more readily available starting material cyclooctene. Each route involves three simple reactions and affords a product that has the new feature of containing a bromine substituent on the methylene bridge, thereby providing a potential capability for structural elaboration at this position.

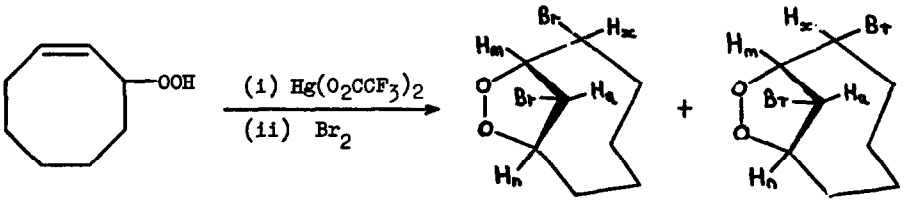
The first step in each method is the conversion of cyclooctene into

2-cyclooctenyl hydroperoxide (2). This has been achieved previously by autoxidation, but a mixture of products was obtained.[2] We have found that tetraphenylporphine-sensitized photooxygenation of cyclooctene in dichloromethane for 9h followed by flash chromatography[3] on silica gel affords an analytically pure product in a yield of about 10%.[4]



2

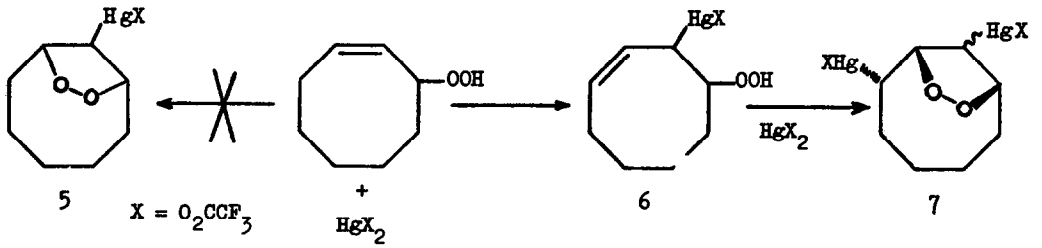
Treatment of 2 with mercury(II) trifluoroacetate in dichloromethane at 0°C, followed by bromodemercuration *in situ* yielded a mixture containing two peroxidic products (TLC). Isolation by preparative HPLC afforded, in order of elution, the *cis*-2, *cis*-10-dibromo-8,9-dioxabicyclo [5.2.1] decane 3 (0.6%; m.p. 66°C) and *trans*-2, *cis*-10-dibromo-8,9-dioxabicyclo [5.2.1] decane 4 (2.7%; m.p. 77°C), which were identified by a combination of elemental analysis, mass spectrometry, and ^1H and proton-decoupled ^{13}C NMR spectroscopy.[5]



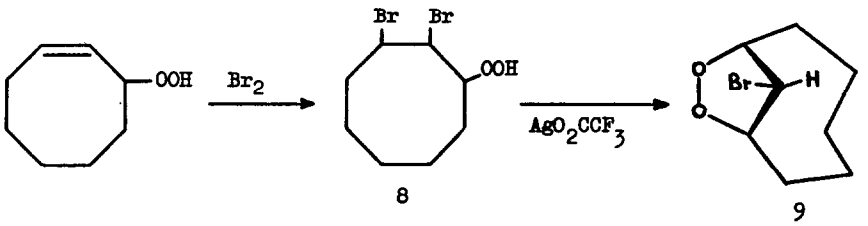
3 4

The stereochemical assignments for 3 and 4 are based on their ^1H NMR spectra.[5] In particular the observation for both isomers that the coupling constants J_{am} and J_{an} are small (1-3Hz) rules out a *trans*-arrangement for the bromine at the 10-position.

It appears that allylic mercuration[6] to give 2-trifluoroacetoxymercurio-3-cyclooctenyl hydroperoxide (6), presumably as a mixture of *cis*- and *trans*-isomers, is preferred to the disfavoured[7] 5-*endo*-cyclization that would afford 10-trifluoroacetoxymercurio-8,9-dioxabicyclo [5.2.1] decane (5). Mercury salt-induced 5-*exo*-cyclization then provides the organomercury precursor (7) of compounds 3 and 4. Bicyclic peroxides with a *trans*-10-substituent could be formed in the cycloperoxymercuration and/or in the bromodemercuration, but none were detected in the final product.



Alternatively, treatment of 2 with bromine in dichloromethane at 0°C yielded a mixture of diastereoisomeric 2,3-dibromocyclooctyl hydroperoxides (8), in the ratio of about 2:1 as judged from the intensity of the ^{13}C NMR signals (δ 86.41 and 82.12) assigned to the carbons bearing the HOO group. Ring closure with silver trifluoroacetate[8,9] gave, after isolation by preparative HPLC, 4.3% of cis-10-bromo-8,9-dioxabicyclo [5.2.1] decane (9) as a colourless viscous oil that slowly crystallised at 0°C.[10]



The cis-arrangement of the bromine substituent and the peroxide bridge in 9 is assumed on the basis of trans-bromination and then inversion of configuration in the dioxabicyclization.[9] Overlap of the CHBr and bridgehead H signals in the 100 MHz ^1H NMR spectrum prevented a determination of the vicinal coupling constant that would confirm this stereochemistry.

Both reaction sequences employed in these new routes to 8,9-dioxabicyclo-[5.2.1] decane derivatives could conceivably give rise also to formation of bicyclic dioxetanes.[6,11] These were not detected but they would not be expected to survive the conditions under which our products were isolated.

Of the two routes reported here, the sequence of singlet oxygenation, bromination, and silver salt-induced dioxabicyclization is probably the more valuable since it proceeds stereospecifically and introduces only one bromine substituent. Furthermore the silver salt-assisted cyclization has previously proved successful in the preparation of sensitive peroxides such as dioxetanes[11] and 2,3-dioxabicyclo-[2.2.1] heptane.[9] We are therefore investigating the generality of this method for converting cycloalkenes into dioxabicyclo [n.2.1] alkanes containing a bromomethylene bridge.

We thank the S.R.C. for financial support and Dr. A.G. Loudon for carrying out the accurate mass measurement on compound 9.

References and Notes

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4. The light source was a 140 W sodium lamp. Compound 2. ^{1}H NMR (60 MHz; $CDCl_3$): δ 1.75 m (10H), 4.85 m (1H), 5.63 m (2H), 9.0 broad s (1H). ^{13}C NMR (20 MHz; $CDCl_3$): δ 23.73, 26.27, 26.58, 29.11, 33.22, 83.99, 131.33, 132.91. Found: C, 67.33; H, 10.04%. $C_8H_{14}O_2$ requires: C, 67.61; H, 9.86%.

5. HPLC was on 25 cm of Partisil 10 using pentane/CH_2Cl_2 (3:1). Compound 3. ^{1}H NMR (100 MHz; $CDCl_3$): δ 1.76 m (6H), 2.36 m (2H), 4.48 m (H_x), 4.76 dd (J = 5 and 1 Hz; H_m), 4.84 q (J = 3 Hz; H_n), 5.2 dd (J = 3 and 1 Hz; H_a). Found: C, 31.96; H, 3.79%. $C_8H_{12}Br_2O_2$ requires: C, 32.00; H, 4.00%. Compound 4. ^{1}H NMR (100 MHz; $CDCl_3$): δ 1.82 m (6H), 2.40 m (2H), 4.26 ddd (J = 8.5, 7, and 1.5 Hz; H_x), 4.70 dd (J = 3 and 1.5 Hz; H_a), 4.80 ddd (J = 6, 3, and 1.5 Hz; H_n); 4.99 t (J = 1.5 Hz; H_m). Double irradiation confirmed that the signal at 4.99 is coupled with those at 4.70 and 4.26, and showed that the signal at 4.26 is coupled with that at 2.40. ^{13}C NMR (20 MHz; $CDCl_3$): 25.33, 26.33, 30.66, 37.69, 52.50, 58.76, 88.88, 93.34. Found: C, 32.49; H, 4.08%. Both isomers showed peaks in MS at m/z = 298 (M^+), 300, and 302 in ratio 1:2:1.

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10. Compound 9. ^{1}H NMR (100 MHz; $CDCl_3$): δ 2.0 m (10H), 4.78 m (3H). ^{13}C NMR (20 MHz; $CDCl_3$): δ 25.31, 25.83, 32.28, 62.04, 88.59. MS: m/z = 220 (M^+) and 222 in ratio 1:1. Found: m/z = 220.0089; $C_8H_{13}{}^{79}BrO_2$ requires m/z = 220.0099.

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(Received in UK 7 December 1978)