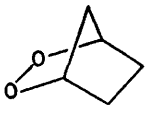
Simple Conversion of Cycloalkenes into Bromo-substituted Prostanoid Endoperoxides (Dioxabicyclo[*n*.2.1]alkanes)

By A. J. BLOODWORTH* and HENNY J. EGGELTE

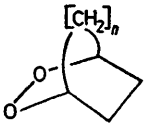
(*Christopher Ingold Laboratories, Chemistry Department, University College London, 20 Gordon Street, London* WC1H 0AJ)

Summary Dioxabicyclo[*n*.2.1]alkanes bearing a *cis*-bromine on the one-carbon bridge are readily prepared from cycloalkenes by the sequence singlet oxygenation, bromination, and treatment with silver trifluoroacetate.

CHEMICAL lability associated with the 2,3-dioxabicyclo-[2.2.1]heptane (**1**) nucleus of prostaglandin endoperoxides is important in the biosynthesis of prostaglandins.[1] To establish which structural features of this nucleus, if any, are necessary to observe the type of chemistry associated with prostaglandin endoperoxides, it is desirable to study the behaviour of a variety of related bicyclic peroxides. Of particular interest are comparisons within homologous series where some features of structure (**1**) are retained by each member while others are varied systematically. The recently discovered combination of singlet oxygenation of cycloalka-1,3-dienes and di-imide reduction provides a general route to dioxabicyclo[*n*.2.2]alkanes (**2**),[2] a series in which each homologue retains the type of 1,2-dioxacyclohexane ring present in (**1**). We now describe the preparation of a new homologous series of endoperoxides that are substituted dioxabicyclo[*n*.2.1]alkanes (**3**), where the 5-membered peroxide ring is the prostanoid feature that is preserved throughout.



(1)



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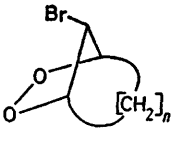
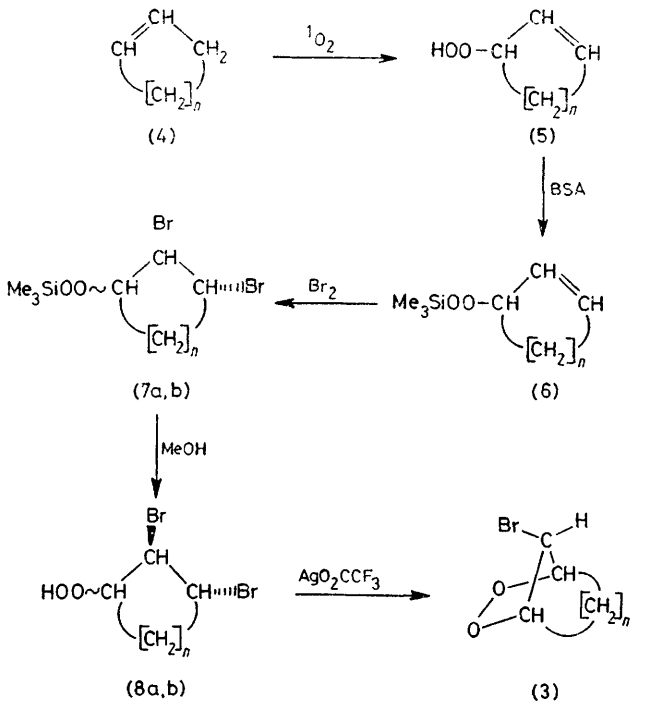


(3)

Our strategy is outlined in the Scheme. Commercially available reagents are used throughout and each step of the procedure is easy to carry out. First, the 2-cycloalkenyl hydroperoxide (**5**) was prepared by photo-oxygenation of the cycloalkene (**4**), neat or in dichloromethane solution, using tetraphenylporphine as sensitizer and a 140 W sodium lamp as light source. The reaction was slow but also clean at the 5—25% conversions obtained after 3—5 days' irradiation. Pure hydroperoxides were thus obtained simply by removing unchanged cycloalkene (and dichloromethane if used) followed by short-path distillation under reduced pressure.

Next, the hydroperoxide was silylated using bistrimethylsilylacetamide (BSA) before carrying out bromine addition in carbon tetrachloride at 0 °C. Methanolysis



SCHEME

then afforded the crude 2,3-dibromocycloalkyl hydroperoxide as a mixture of *cis–trans* (**8a**) and *trans–trans* (**8b**) diastereoisomers. Intermediates (**6**) and (**7**) were not isolated and an almost quantitative conversion of (**5**) into (**8**) was achieved. Purification of (**8**) by column chromatography (SiO_2–CH_2Cl_2) also effected partial separation of the diastereoisomers.

The advantages of adding bromine to the trimethylsilyl peroxide (**6**) rather than directly to the hydroperoxide (**5**) are twofold. First it reduces the formation of side products arising from (mainly intermolecular) attack of peroxide upon the intermediate bromonium ion, and secondly it increases the fraction obtained of *cis–trans*-2,3-dibromocycloalkyl hydroperoxide (**8a**) which is the isomer that ring-closes to give endoperoxide in the final step. Both effects were particularly dramatic with the cyclohexenyl system.

The ring closure was carried out by stirring (**8**) with silver trifluoroacetate in dichloromethane for 1 h at room temperature. The endoperoxide (**3**) was readily separated from the more polar components of the mixture, including unchanged hydroperoxide and products of trifluoroacetate-for-bromine substitution, by low temperature column chromatography (SiO_2–CH_2Cl_2; *ca.* −35 °C) and was purified by recrystallisation (light petroleum–CH_2Cl_2) at low temperature.

TABLE. Prostanoid endoperoxides (**3**)[a]

n	M.p./°C	Yield/%[b]	^{13}C n.m.r.[c] δ(Me_4Si)/p.p.m.
2	52—53	13	82·36, 55·12, 27·85
3	72—74	27	82·89, 60·39, 32·07, 16·06
4	76—77	38	87·50, 57·40, 32·57, 22·63
5	64—65	13	88·59, 62·04, 32·28, 25·83, 25·31

[a] Satisfactory C, H, and Br analyses were obtained for each compound, and mass spectra showed the expected M^+ and $(M + 2)^+$ ions. [b] Of isolated peroxide. Based on cycloalkenyl hydroperoxide (**5**). [c] $CDCl_3$ solution.

The bicyclic peroxides obtained are shown in the Table. Further evidence of structure was provided by ^{1}H n.m.r. spectroscopy. For the [2.2.1]-endoperoxide the absence of long range W-plan coupling for the C*H*Br proton shows that the bromine is *cis* to the peroxide linkage and confirms that, as expected,[3] the dioxabicyclization takes place with inversion of configuration. It is assumed that this holds also for the other three systems.

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[3] N. A. Porter and D. W. Gilmore, *J. Amer. Chem. Soc.*, 1977, **99**, 3503.