Prostaglandin Endoperoxide Model Compounds. Part 1. Synthesis of (*n* + 5)-Bromodioxabicyclo[*n*.2.1]alkanes [1]

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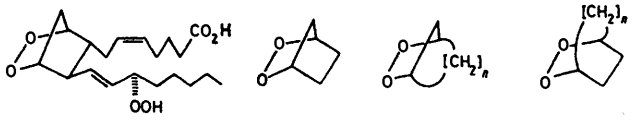
Four *cis*-(*n* + 5)-bromodioxabicyclo[*n*.2.1]alkanes (12) (*n* = 2—5) have been prepared from C_6–C_8 cycloalkenes by the sequence singlet oxygenation, bromination, and treatment with silver trifluoroacetate.

Photo-oxygenation of cycloalkenes provides a convenient route to the corresponding cycloalk-2-enyl hydroperoxides (6). Bromination of each of these proceeds smoothly in carbon tetrachloride to afford a mixture of *cis*-2,*trans*-3-dibromocycloalkyl hydroperoxide (10) and *trans*-2,*cis*-3-dibromocycloalkyl hydroperoxide (11). Except for 2,3-dibromocyclo-octyl hydroperoxide, the major isomer obtained is (10) and the fraction of (10) in the mixture can be increased by silylating (6) with bistrimethylsilylacetamide before bromination and afterwards desilylating the dibromo-adducts by methanolysis. Both (10) and, less efficiently, (11) react with silver trifluoroacetate to give compounds (12), which are readily separated by low-temperature column chromatography from the bromo-trifluoroacetoxy-cycloalkyl hydroperoxides concurrently formed.

Configurational assignments for (10), (11), and (12) have been made on the basis of spectroscopic data and chemical reactions.

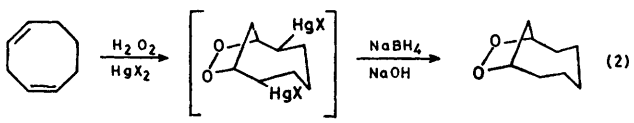
PROSTAGLANDINS, thromboxanes, and other physiologically active substances are formed in mammalian tissue by oxidation of polyunsaturated fatty acids. Prostaglandin endoperoxides [*e.g.* (1)] are key intermediates in this process, since at this point the biosynthetic pathway diverges because the 2,3-dioxabicyclo-[2.2.1]heptane nucleus may readily participate in several alternative transformations.[2]



(1) (2) (3) (4)

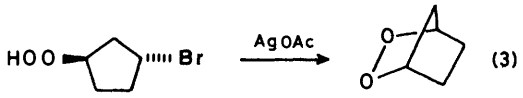
To place the peroxide chemistry associated with this biosynthesis on a firm basis, it is necessary to prepare, and study the reactions of, model bicyclic peroxides. Prime interest obviously surrounds 2,3-dioxabicyclo-[2.2.1]heptane (2) and its simple derivatives, but comparisons with higher homologues should help to establish which features of the [2.2.1] system, if any, are necessary for the type of chemistry associated with prostaglandin endoperoxides to be observed. It is therefore appropriate to develop methods for preparing homologous series of bicyclic peroxides in which either the 5- or the 6-membered peroxide ring of (2) is retained by each member, *i.e.* dioxabicyclo[*n*.2.1]alkanes (3) and dioxabicyclo[*n*.2.2]alkanes (4).

The recent discovery that di-imide will hydrogenate the double bond of singlet oxygen adducts of cycloalka-1,3-dienes while preserving the peroxide linkage has provided a general route [equation (1)] to compounds (*n* = 1—4) of series (4).[3] Our aim was to complement this by developing a general procedure for obtaining peroxides of the [*n*.2.1] series (3). We were able to prepare 8,9-dioxabicyclo[5.2.1]decane (3, *n* = 5) by peroxymercuration and reduction of cyclo-octa-1,4-diene [equation (2)];



(2)

X = O_2CCF_3],[4] but attempts to extend the method to other members of the series proved unsuccessful.[5] Hence we turned our attention to attempts to exploit other newly developed methods for preparing dialkyl peroxides under mild conditions.[6] The silver salt-assisted alkylation technique [7] was an obvious choice since it has provided a successful route [equation (3)] [8]



(3)

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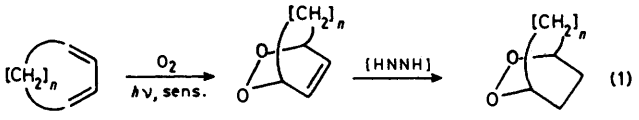
to 2,3-dioxabicyclo[2.2.1]heptane (2). We now give full details [1] of a procedure that incorporates a similar silver salt-induced dioxabicyclization in bringing about a simple conversion of cycloalkenes into (*n* + 5)-bromodioxabicyclo[*n*.2.1]alkanes, *i.e.* peroxides of type (3) that bear a bromine atom on the one-carbon bridge.

RESULTS AND DISCUSSION

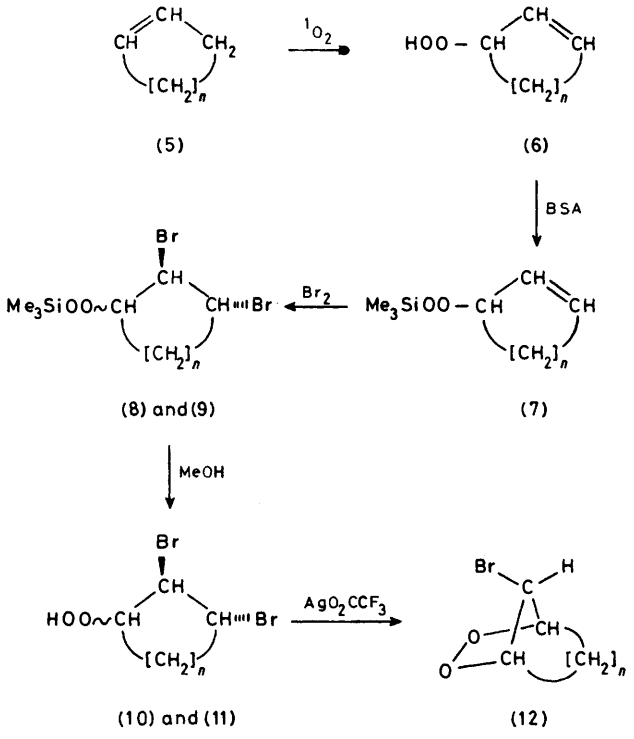
Design of Synthetic Pathway.—In seeking a general route to dioxabicyclo[*n*.2.1]alkanes (3), we looked for a sequence of reactions that would convert readily available starting materials into cycloalkanes carrying hydroperoxy- and bromo-substituents in the 1,3-*trans*-relationship known [*cf.* equation (3)] [8] to be suitable for silver salt-induced bicyclization. The strategy we developed is outlined in the Scheme.



(1)

(4)

The hydroperoxy-group was introduced by photo oxygenation [9] of the cycloalkenes (5) and the 3-bromo-substituent was incorporated by bromination of the



SCHEME

a; $n = 2$
b; $n = 3$
c; $n = 4$
d; $n = 5$

resulting cycloalk-2-enyl hydroperoxides (6). Although 2,3-dibromocycloalkyl hydroperoxides contain three chiral centres, the occurrence of normal *trans*-addition ensured that only the desired *cis*-2,*trans*-3-dibromocycloalkyl hydroperoxides (10) and the unwanted *trans*-2,*cis*-3-dibromocycloalkyl hydroperoxides (11) were formed. The bromination was markedly sensitive to conditions but by carrying out the reaction in carbon tetrachloride at 0 °C good yields of (10) and (11) were obtained and, except for the cyclo-octyl compound, (10) was the major product. A modification that, except for the 8-membered ring compound, promoted a cleaner conversion of (6) into (10) and (11) and afforded a higher proportion of the desired (10) was to carry out the bromination on the trimethylsilyl derivatives (7) obtained by treating (6) with bistrimethylsilylacetamide (BSA). Desilylation of the bromination adducts (8) and (9) was readily effected by methanolysis and it was unnecessary to isolate the trimethylsilyl compounds. In this way the bromination adducts of the 6- and 7-membered rings (6b) and (6c) were obtained in virtually quantitative yield and impurities were barely detectable. The reactions with the 5- and 8-membered rings (6a) and (6d) were less successful, the 2,3-dibromocyclopentyl hydroperoxides being contaminated with 10—15% of the corresponding alcohols and the 2,3-dibromocyclo-octyl hydroperoxides containing 20—25% of largely unidentified impurities.

Silver trifluoroacetate was used to induce the dioxabicyclizations. Competing substitution afforded bromotrifluoroacetoxycycloalkyl hydroperoxides but the relatively short chromatographic retention times for the $(n + 5)$-bromodioxabicyclo[n.2.1]alkanes (12) enabled them to be separated from these by-products and from unchanged (10) and (11) without difficulty.

The 2,3-dibromocycloalkyl hydroperoxides could be purified by chromatography and this also provided samples highly enriched in (10). However use of the crude compounds gave better overall yields for the conversion of (6) into (12) (Table 1). The only problem then encountered was that some fractions of (12b) were contaminated with small amounts of 2,3-dibromocyclohexanone, but this was easily removed by recrystallisation.

The main reason for the low yield (16%) of (12a) was that trifluoroacetate incorporation is particularly prevalent with the 5-membered ring. Accordingly we investigated the use of silver oxide in this dioxabicyclization. This modification proved highly successful, affording a vastly improved yield (43%) of (12a) and also providing a sample (16%) of isomerically pure (11a) that was required for later studies on the individual reactivities of (10) and (11) towards silver trifluoroacetate. The yield of (12d) was similarly improved by replacing silver trifluoroacetate with the oxide, but here the effect was less dramatic since the predominance of the unwanted (11d) is more influential than the competing trifluoroacetate incorporation in determining the efficiency of ring closure.

Although the isomers (11) have hydroperoxy- and

TABLE 1

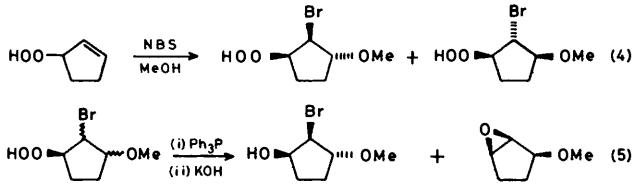
$(n + 5)$-Bromodioxabicyclo[n.2.1]alkanes (12)

				Found (%) [a]			Calc. (%)		
n	Cmpd.	M.p. (T/°C) [a]	Yield(%) [b]	C	H	Br	C	H	Br
2	(12a)	52—53 [c]	16 (43) [e]	33.6	3.9	45.0	33.55	3.9	44.6
3	(12b)	72—74 [c]	56	37.0	4.75	42.1	37.3	4.7	42.1
4	(12c)	76—77 [d]	38	40.4	5.3	38.1	40.6	5.4	38.6
5	(12d)	64—65 [d]	13 (18) [e]	43.4	6.0	36.2	43.5	5.9	36.1

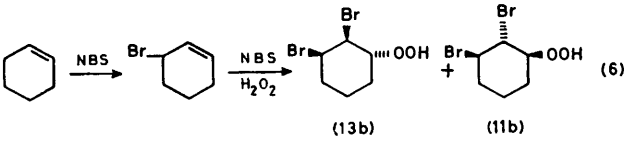
[a] For recrystallised sample. [b] Of spectroscopically pure (12) obtained according to the Scheme and isolated by column chromatography. Based on conversion from cycloalk-2-enyl hydroperoxide (6). [c] From pentane and CH_2Cl_2 at −78 °C. [d] From hexane at 0 °C. [e] Using Ag_2O in the dioxabicyclization step and omitting the silylation.

bromo-substituents in the *trans*-1,2 relationship appropriate for dioxetan formation,[10] we found no evidence for such a cyclization with any of the four systems studied.

We envisaged the possibility of modifying the sequence by treating the cycloalkenyl hydroperoxides (6) with *N*-bromosuccinimide (NBS) in nucleophilic solvents to



provide the precursors of other $(n + 5)$-substituted-dioxabicyclo[n.2.1]alkanes. However the two diastereoisomeric bromo-methoxy-cyclopentyl hydroperoxides obtained in this way failed to react with silver trifluoroacetate during 64 h at room temperature. We concluded that the methoxy-group had entered in the 3-position [equation (4)], and we obtained evidence to support this by generating an epoxide from the corresponding mixture of alcohols afforded by reduction with triphenylphosphine [equation (5)]. The alcohol that did not epoxidise underwent elimination slowly to give cyclopent-2-enone.

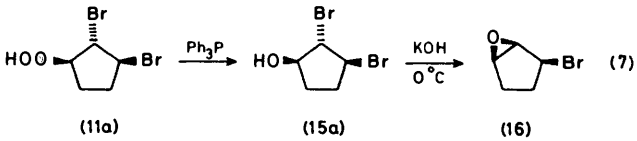


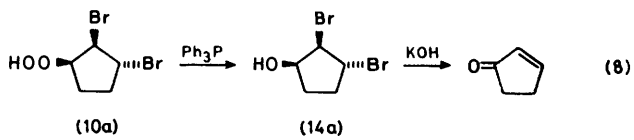
Another sequence we investigated involved the preparation of the cycloalk-2-enyl bromide followed by reaction with an electrophile in the presence of hydrogen peroxide. In this way we obtained a mixture of *trans*-2,*cis*-3-dibromocyclohexyl hydroperoxide (11b) (overlap with products from bromination of cyclohex-2-enyl hydroperoxide) and a diastereoisomer believed to be *trans*-2,*trans*-3-dibromocyclohexyl hydroperoxide (13b) [equation (6)]. We hoped that (13b) would ring-close to give a diastereoisomer of (12b) in which the bromine was *trans* to the peroxide bridge, but it failed to react with silver trifluoroacetate.

Although these reactions proved unsuccessful as far as the synthesis of bicyclic peroxides is concerned, they provided information that is helpful in suggesting a probable mechanism for the bromination of cycloalk-2-enyl hydroperoxides (see later).

Stereochemical Considerations.—(a) *Configurations of the 2,3-dibromocycloalkyl hydroperoxides.* The diastereoisomers of the 2,3-dibromocycloalkyl hydroperoxides were best distinguished by their ^{13}C n.m.r. spectra (Table 2).

The configurations of the diastereoisomeric 2,3-dibromocyclopentyl hydroperoxides were determined by

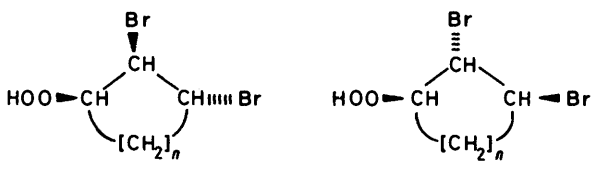




identifying which of the corresponding alcohols (14a) and (15a), obtained by configuration-preserving reduction with triphenylphosphine, reacted with base to give 2,3-epoxycyclopentyl bromide (16), for this must be formed from the isomer (15a) with the 2-bromine *trans* to the OH group [equation (7)]. Thus when a mixture

TABLE 2

^{13}C N.m.r. spectra of 2,3-dibromocycloalkyl hydroperoxides

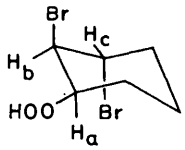


n	Isomer	C–OO	C–Br		δ(Me$_4$Si)/p.p.m. [a] Others				
2	(10a)	84.55	59.34	53.05	32.03	24.87			
	(11a)	92.94	56.02	53.08	33.87	27.74			
3	(10b)	78.65	55.02	52.04	28.11	24.32	19.38		
	(11b)	85.56	56.25	53.39	35.61	28.14	21.43		
	(13b) [b]	84.08	55.51	52.78	32.74	25.40	21.05		
4	(10c)	82.17	58.96	54.58	32.85	26.69	22.02	21.77	
	(11c)	89.09	57.42	57.30	33.24	27.46	25.94	22.40	
5	(10d)	82.28	60.01	57.23	31.07	29.36	26.39	24.18	23.39
	(11d)	86.17	59.81	58.31	33.86	29.28	26.02	24.63	22.95

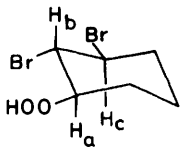
[a] $CDCl_3$ solution. [b] Major isomer from reaction of cyclohex-2-enyl bromide with NBS and hydrogen peroxide; believed to be *trans*-2,*trans*-3-dibromocyclohexyl hydroperoxide.

of 2,3-dibromocyclopentyl hydroperoxides containing 67% of the isomer characterised by $\delta(^{13}COOH) = 84.55$ p.p.m. was converted into the alcohols and treated with potassium hydroxide at 0 °C, the less abundant isomer was completely consumed, (16) was formed, and a large fraction of the more abundant alcohol was recovered. Some cyclopent-2-enone was also obtained and it was confirmed in an independent experiment that this is formed slowly from the major alcohol [equation (8)].

The configuration of the major isomer of 2,3-dibromocyclohexyl hydroperoxide [$\delta(^{13}COOH) = 78.65$ p.p.m.] was established from its ^1H n.m.r. spectrum. The favoured conformation for (10b) is expected to be that with equatorial OOH and diaxial bromines, while a triequatorial conformation should be favoured for (11b).



(10b)



(11b)

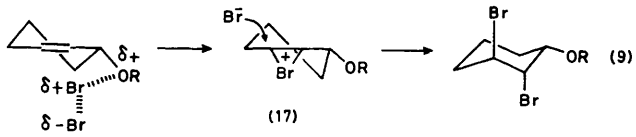
At 100 MHz separate signals were observed for H_a, H_b, and H_c and could be assigned on the basis of their chemical shifts. The multiplet for H_a was broad ($W_{\frac{1}{2}} = 16$ Hz) while those for H_b and H_c were narrow ($W_{\frac{1}{2}} = 7$ and 8 Hz respectively), clearly pointing to structure (10b). This conclusion was confirmed by reducing the hydroperoxide with triphenylphosphine to the known [11] *cis*-2,*trans*-3-dibromocyclohexanol, though it should be pointed out that the configurational assignment for the alcohol was similarly based on ^1H n.m.r. spectroscopic data.

Evidence to support the assignment of configuration (11) to the 2,3-dibromocyclohexyl hydroperoxide [$\delta(^{13}COOH) = 85.56$ p.p.m.] formed in lower yield came from the fact that it was also obtained from the reaction of cyclohex-2-enyl bromide with *N*-bromosuccinimide and hydrogen peroxide [equation (6)]. Assuming that *trans*-addition takes place in both bromination (Scheme) and hydroperoxybromination [equation (6)], then only (11b) can be common to both routes.

Although configurational assignments based on ^1H n.m.r. spectra are less reliable for 7-membered rings than for cyclohexane derivatives, the data for the major isomer of 2,3-dibromocycloheptyl hydroperoxide [$\delta(^{13}COOH) = 82.17$ p.p.m.] were indicative of structure (10). For the 5- and 6-membered rings it was shown that isomer (10) gives a better yield of bicyclic peroxide upon reaction with silver trifluoroacetate than does isomer (11) (see later). The configurational assignments for the 2,3-dibromocycloheptyl hydroperoxides were confirmed and those for the 2,3-dibromocyclo-octyl hydroperoxides were made on the assumption that similar considerations hold also for the larger rings.

A further indication that all the configurational assignments made as described above are correct comes from the observation of a consistent pattern in the ^{13}C n.m.r. spectroscopic data (Table 2). Thus the isomer (10) has $\delta(^{13}COOH)$ at higher field than does isomer (11) for all four systems, a result that is compatible with the shielding effects of the bromine atoms being related to their stereochemical disposition.

It is noteworthy that the ratios (3 : 1 and 6 : 1) of diastereoisomers obtained in the bromination of cyclohex-2-enyl hydroperoxide and its trimethylsilyl derivative are similar to those (4 : 1) obtained [11] previously for cyclohex-2-enol and its methyl ether. The latter results were interpreted [11] in terms of a mechanism in which nucleophilic attack by Br^- is strongly directed to the 3-position by the inductive effect, and product distribution is dictated by a preference to form the *cis*-bromonium ion as a result of complexation of the bromine by the oxy-substituent [equation (9), R = H or Me]. A similar mechanism [equation (9), R = OH or $OSiMe_3$] can be offered for bromination of the cyclohex-2-enyl peroxides, and the possibility of bromine complexation with the second oxygen atom now also exists. That nucleophilic attack occurs at the 3-position of the bromonium ion (17; R = OH) was indicated by the



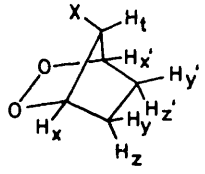
reaction of cyclohex-2-enyl hydroperoxide with *N*-bromosuccinimide in methanol. This afforded essentially just one bromo-methoxycyclohexyl hydroperoxide and it did not react with silver trifluoroacetate, which suggests that the methoxy-group had entered in the 3-position; compare this with the analogous reaction of cyclopentenyl hydroperoxide [equation (4)] where the structure of the adduct was supported by further evidence.

It seems likely that the same mechanism also operates in the bromination of cyclopentenyl and cycloheptenyl hydroperoxides in view of the similarity of the stereochemical results to those obtained for the cyclohexenyl compound. However the bromination of cyclo-octenyl hydroperoxide differs in that it is essentially unaffected by silylation and appears to favour the *trans*-2,*cis*-3-dibromo-isomer [ratio (10) : (11) = 1 : 2]. Presumably the mechanism is modified as a result of the greater flexibility of the 8-membered ring.

(b) *Configurations of the* (n + 5)*-bromodioxabicyclo*[n.2.1]*alkanes* (12). Only *one* bicyclic peroxide was obtained for each ring system, irrespective of the ratio of diastereoisomers (10) and (11) in the 2,3-dibromocycloalkyl hydroperoxide precursor. That these were (*n* + 5)-bromodioxabicyclo[*n*.2.1]alkanes (12) was elegantly demonstrated by ^{13}C n.m.r. spectroscopy. The spectrum of each peroxide showed the number of lines appropriate to the symmetry of (12) and contained a single resonance in the region δ 55—62 p.p.m. which can

be assigned with confidence to the one-carbon bridge by comparison with the data for 2,3-dioxabicyclo[2.2.1]-heptane [8] and 8,9-dioxabicyclo[5.2.1]decane,[4] bearing in mind the well known α-effect of a bromine substituent. The presence of the bromine in (12) was confirmed by elemental analysis (Table 1) and mass spectrometry.

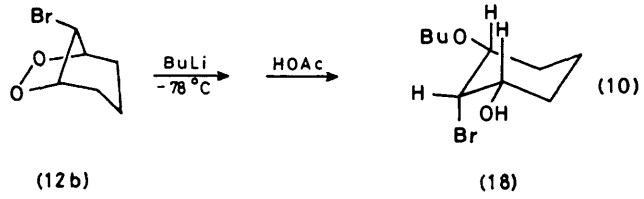
There remains the question of whether the (*n* + 5)-bromine is *cis* or *trans* to the peroxide bridge. The configuration of 7-bromo-2,3-dioxabicyclo[2.2.1]heptane (12a) was established from its ^{1}H n.m.r. spectrum. In 2,3-dioxabicyclo[2.2.1]heptane (2) the 7-hydrogen (H_c) *cis* to the peroxide bridge is distinguished from its geminal neighbour (H_t) by the fact that it shows long range W-plan coupling (to H_z and $H_{z'}$).[3] Since the 7-hydrogen in our bromoperoxide appeared as a singlet it must be *trans* to the peroxide bridge, and hence the bromine must be *cis* as indicated in formula (12).



(2) X = Hc

(12a) X = Br

The configuration of 8-bromo-6,7-dioxabicyclo[3.2.1]-octane (12b) was determined by establishing the structure of the 2-bromo-3-butoxycyclohexanol (18) obtained quantitatively by cleaving the peroxide bond with butyl-lithium [equation (10)]. The narrow multiplet



(10)

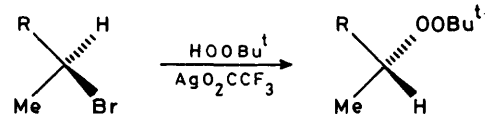
(12b) (18)

($W_{\frac{1}{2}}$ = 6 Hz) obtained for C*H*Br in the ^{1}H n.m.r. spectrum of (18) clearly pointed to the all-*cis* configuration in the expected conformation with bromine disposed axially.

The [4.2.1]- and [5.2.1]-bromoperoxides have been assigned the same *cis*-configuration as the [2.2.1]- and [3.2.1]-compounds on the assumption that the mechanism of dioxabicyclization (see below) is unchanged for the larger rings.

(c) *Stereochemistry of dioxabicyclization.* We have established that bromination of cyclopentenyl and cyclohexenyl hydroperoxides affords predominantly the *cis*-2,*trans*-3-dibromocycloalkyl hydroperoxides (10), and that these, mixed with small amounts of the corresponding *trans*-2,*cis*-3-dibromo-isomers (11), each react with silver trifluoroacetate to afford a *cis*-(*n* + 5)-bromodioxabicyclo[*n*.2.1]alkane and no other bicyclic peroxide. The simplest interpretation of these results is that dioxabicyclization occurs by displacement of the 3-bromine in (10) with inversion of configuration, the stereochemistry at the 2-position being unaffected.

This conclusion is in keeping with previous observations on the stereochemistry of silver salt-assisted alkylation of hydroperoxides. Thus 1-phenylethyl and 1-methylheptyl bromide reacted with t-butyl hydro-



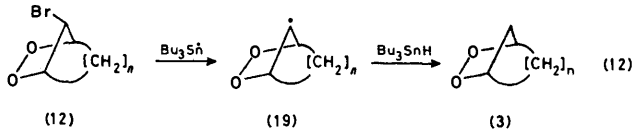
(11)

peroxide and silver trifluoroacetate to give the secondary-alkyl t-butyl peroxides with predominant inversion [equation (11), R = Ph or C_6H_{13}].[12] More directly related to our work was the demonstration that *cis*-3-bromocyclopentyl hydroperoxide reacted only slowly with silver salts to give a poor yield of 2,3-dioxabicyclo-[2.2.1]heptane whereas the conversion proceeded rapidly and quantitatively with the *trans*-isomer [equation (3)].[8]

The situation is less straightforward than at first appears, however, for our results show that the bicyclic peroxides (12) are also formed from the *trans*-2,*cis*-3-dibromocycloalkyl hydroperoxides (11), albeit less efficiently than from (10). Thus samples of (11a), (11b), and (11d), which contained none of the corresponding isomers (10), afforded the appropriate bicyclic compound (12) in yields of 10, 19, and 9% respectively. We feel that the transformation of (11) into (12) probably proceeds *via* an initial isomerisation to (10) rather than by displacement of the 3-bromine with retention of configuration (*cf.* the result with *cis*-3-bromocyclopentyl hydroperoxide [8]) followed by inversion at the one-carbon bridge of the resulting *trans*-(*n* + 5)-bromodioxabicyclo-[*n*.2.1]alkane.

Reactions of (n + 5)-*Bromodioxabicyclo*[n.2.1]*alkanes.*— We carried out a brief investigation to see if the bromine in the endoperoxides could be replaced. Nucleophilic substitution is expected to be unfavourable because backside attack is inhibited by the presence of the carbocyclic ring and considerable extra strain must be introduced into the system to force an inversion. The absence of any trifluoroacetoxy-substituted bicyclic peroxides in the products of ring-closure already supports this supposition and it was confirmed by the fact that *cis*-10-bromo-8,9-dioxabicyclo[5.2.1]decane (12d) was recovered unchanged from prolonged exposure to silver trifluoroacetate in dichloromethane (for 64 h), in methanol (for 2 h), and in dichloromethane containing t-butyl hydroperoxide (for 5 h).

We hoped that we might be able to replace the bromine



(12) (19) (3) (12)

by a free-radical reduction with tributyltin hydride [equation (12)]. If successful, such a reaction would permit the series of parent dioxabicyclo[*n*.2.1]alkanes (3) to be prepared. We were encouraged by the fact

that the geometry of the intermediate alkyl radicals (19) is unfavourable for intramolecular attack on the peroxide bond [13] and hence γ-scission to form epoxides should not compete seriously with the desired hydrogen abstraction.

A reaction between tributyltin hydride and the [3.2.1]-bromo-peroxide (12b) took place in benzene at 40—50 °C, but no 6,7-dioxabicyclo[3.2.1]octane was detected among the products. The tin-free material which was isolated was non-peroxidic and is believed to be a mixture; spectroscopic data (^{1}H and ^{13}C n.m.r. and i.r.) suggested the presence of alcohol and aldehyde functions and, more significantly, of bromoalkyl groups. It appears that cleavage of the peroxide linkage is at least partially preferred to reduction of the bromide under the conditions used. No reaction occurred at room temperature.

EXPERIMENTAL

Silver trifluoroacetate was prepared from silver oxide and trifluoroacetic acid as described previously [14] and was stored in the dark. Unless indicated to the contrary, all other reagents and solvents were commercial samples that were used without further purification.

^{1}H N.m.r. spectra were recorded at 100 MHz for solutions in deuteriochloroform using a Varian HA100 spectrometer, or at 60 MHz for solutions in carbon tetrachloride using a Perkin-Elmer R12 instrument. ^{13}C (Natural abundance) n.m.r. spectra were recorded at 20 MHz for solutions in deuteriochloroform using a Varian CFT 20 spectrometer. I.r. spectra were recorded for *ca.* 7% solutions in carbon tetrachloride using a Perkin-Elmer 457 spectrometer with potassium bromide optics. Mass spectra were obtained with an A.E.I. MS12 instrument (inlet temperature <70 °C).

Column chromatography was carried out using Merck silica (70—230 mesh; 20—30 g per g of product) with dichloromethane as eluant. The solvent was removed *in vacuo* from each fraction (10—20 cm^3) and the residue, or if necessary the combined residue from successive fractions, was examined by n.m.r. spectroscopy. The presence of peroxide in the eluant was monitored by regular testing with acidified iron(II) thiocyanate.[5]

All organic peroxides obtained were stored at or below 0 °C.

Preparation of Cycloalk-2-enyl Hydroperoxides (6).—Oxygen was gently bubbled through a stirred solution of the cycloalkene (50 cm^3) in dichloromethane (100 cm^3) containing tetraphenylporphin (5 mg) and the solution irradiated with a 400 W sodium lamp for 1—3 days, more tetraphenylporphin (5 mg) being added at 24 h intervals. A 140 W sodium lamp was also used but longer reaction times were then required to achieve similar conversions (25—50%). Cyclopentenyl, cyclohexenyl, and cycloheptenyl hydroperoxides (6a—c respectively) were isolated by removing the solvent and unchanged cycloalkene at 12 mmHg and were purified by short-path distillation at 60—100 °C (bath) and 1.0—0.1 mmHg. Cyclo-octenyl hydroperoxide (6d) was purified by chromatography on silica gel as described previously.[15] ^{1}H N.m.r. (60 MHz): (6a) δ 1.75—2.20 (m, CH_2), 2.20—2.60 (m, CH_2), 5.05 (m, CHOO), 5.7—6.0 (m, CH=), 6.0—6.25 (m, CH=), and 9.85 br (s, OH); (6b) δ 1.4—2.15 (m, 6 H), 4.45 (m, CHOO), 5.55—6.15 m (C*H*=C*H*), and 8.75 (s, OH); (6c) δ 1.35—2.35 (m, 8 H), 4.6 (m, C*H*OO), 5.7—5.95 (C*H*=C*H*), and 8.7 br (s, OH); (6d) δ 1.35—1.85 (m, 7 H), 1.85—2.35 (m, 3 H), 4.9 (m, CHOO), 5.5—5.8 m (m, C*H*=C*H*), and 9.15 br (s, OH); ^{13}C n.m.r.: (6a) δ 139.11, 128.26, 91.01, 31.29, and 28.01; (6b) δ 134.18, 124.36, 78.62, 26.45, 25.45, and 18.47; (6c) δ 133.18, 131.24, 85.12, 30.93, 28.59, 26.80, and 26.72; (6d) δ 132.91, 131.33, 83.99, 33.22, 29.11, 26.58, 26.27, and 23.73 p.p.m.

Preparation of 2,3-Dibromocycloalkyl Hydroperoxides.—Bistrimethylsilylacetamide (1.9 cm^3; 7.7 mmol) was added to a solution of the cycloalk-2-enyl hydroperoxide (6) (15 mmol) in carbon tetrachloride (10 cm^3) at 0 °C and the mixture was stirred for 1 h at room temperature while protected with a calcium chloride tube. The resulting precipitate of acetamide was filtered off, the filtrate diluted with carbon tetrachloride (60 cm^3) and cooled in an ice-bath, and a solution of bromine (0.85 cm^3) in carbon tetrachloride (20 cm^3) was added dropwise with stirring during 45 min. The mixture was stirred for 30 min at room temperature, methanol (25 cm^3) was added, and stirring was continued for a further 30 min. The volatile materials were removed at 12 mmHg to afford the crude 2,3-dibromocycloalkyl hydroperoxide as a pale yellow oil. Some reactions were carried out on double this scale without difficulty.

The ^{13}C n.m.r. spectra of these crude 2,3-dibromocycloalkyl hydroperoxides and the corresponding products obtained when the silylation and desilylation steps were omitted, were recorded to provide a rough measure of the isomer ratio (10):(11) (see below) and the degree of purity of the adducts (see Discussion section). Each 2,3-dibromocycloalkyl hydroperoxide was purified by column chromatography and this also afforded samples highly enriched in (10) or (11). The recoveries were 60—80% for the 6- and 7-membered rings and 40—50% for the 5- and 8-membered rings. A small amount of fast-running material isolated from the cyclohex-2-enyl hydroperoxide bromination product was identified as 2,3-dibromocyclohexanone; ^{1}H n.m.r. (60 MHz) δ 1.8—3.4 (m, 6 H), 4.5 (m, $W_{\frac{1}{2}}$ 6 Hz, CHBr), and 4.75 (m, $W_{\frac{1}{2}}$ 8 Hz, CHBr); i.r. $\nu_{C=O}$ 1 727 cm^{-1}.

Details for the individual components are given below except for the ^{13}C n.m.r. spectroscopic data which appear in Table 2.

(a) 2,3-*Dibromocyclopentyl hydroperoxide*. The ratio of (10a) to (11a) in the crude adduct was 1.5 : 1 (without silylation) and 3 : 1 (with silylation). Compound (10a) chromatographs faster than (11a), but only isomerically enriched samples were isolated. For (10a) containing *ca.* 15% of (11a): ^{1}H n.m.r. (100 MHz) δ 1.68—1.98 (m, 1 H), 2.02—2.48 (m, 2 H), 2.64—2.96 (m, 1 H), 4.56 (m, $W_{\frac{1}{2}}$ 10 Hz, 3-CHBr), 4.70 (m, $W_{\frac{1}{2}}$ 9 Hz, 2-CHBr), 4.97 (m, $W_{\frac{1}{2}}$ 22 Hz, CHOO), and 8.69 br (s, OH); i.r. ν_{OH} 3 520, and 3 440 cm^{-1} (Found: C, 23.9; H, 3.0; Br, 61.3. Calc. for $C_5H_8Br_2O_2$ C, 23.1; H, 3.1; Br, 61.5%).

(b) 2,3-*Dibromocyclohexyl hydroperoxide*. The ratio of (10b) to (11b) in the crude adduct was 3 : 1 (without silylation) and 6 : 1 (with silylation). Compound (10b) chromatographs faster than (11b) and was isolated isomerically pure. For (10b): ^{1}H n.m.r. (100 MHz) δ 1.40—2.78 (m, 6 H), 4.40—4.68 (m, $W_{\frac{1}{2}}$ 16 Hz, CHOO), 4.78 (m, $W_{\frac{1}{2}}$ 8 Hz, 3-CHBr), 5.02 (m, $W_{\frac{1}{2}}$ 7 Hz, 2-C*H*Br), and 8.48 br (s, O*H*); i.r. ν_{OH} 3 530 and 3 440 cm^{-1} (Found: C, 26.6; H, 3.7; Br, 58.5. $C_6H_{12}Br_2O_2$ requires: C, 26.3; H, 3.7; Br, 58.3%).

(c) 2,3-*Dibromocycloheptyl hydroperoxide*. The ratio of (10c) to (11c) in the crude adduct was 5 : 1 (without silyl-

ation) and 9 : 1 (with silylation). Compound (11c) chromatographs faster than (10c) and both were isolated isomerically pure. For (10c): ^{1}H n.m.r. (100 MHz) δ 1.5—2.10 (m, 6 H), 2.10—2.50 (m, 2 H), 4.52 (m, $W_{\frac{1}{2}}$ 14 Hz, CHOO), 4.78 (m, $W_{\frac{1}{2}}$ 10 Hz, 3-CHBr), 5.22 (m, $W_{\frac{1}{2}}$ 8 Hz, 2-CHBr), and 8.94 br (s, OH); i.r. ν_{OH} 3 530 and 3 430 cm^{-1} (Found: C, 29.6; H, 4.1; Br, 55.7. $C_7H_{12}Br_2O_2$ requires: C, 29.2; H, 4.2; Br, 55.5%); for (11c): ^{1}H n.m.r. (60 MHz) δ 1.5—2.5 (m 8 H), 4.45—4.85 (m, 2 H), 4.85—5.05 (m, 1 H), and 8.45 br (s, OH).

(d) 2,3-*Dibromocyclo-octyl hydroperoxide*. The ratio of (10d) to (11d) in the crude adduct was 1 : 1.7 (without silylation) and 1 : 2 (with silylation). Compound (11d) chromatographs faster than (10d), and was isolated isomerically pure. For (11d): ^{1}H n.m.r. (60 MHz) δ 1.4—1.9 (m, 5 H), 1.9—2.7 (m, 5 H), 4.2—4.95 (m, 3 H), and 8.95 br (s, OH).

Preparation of (n + 5)-*Bromodioxabicyclo*[n.2.1]*alkanes* (12).—A mixture of the 2,3-dibromocycloalkyl hydroperoxide [5 mmol; mixture of diastereoisomers (10) and (11)] and silver trifluoroacetate (1.1 g, 5 mmol) in dichloromethane (50 cm^3) was stirred for 1 h in the dark. The mixture was filtered and the solvent removed from the filtrate at 12 mmHg; the resultant residue was taken up in carbon tetrachloride (15 cm^3), the solution filtered, and the solvent removed at 12 mmHg to afford the crude product.

The endoperoxides (12) were isolated by column chromatography at low temperature. Methylated spirit at −20 to −30 °C was circulated through a vacuum-lined jacket surrounding the column. Each compound (12) chromatographed much faster than the hydroperoxides (starting material or bromotrifluoroacetoxy-cycloalkyl hydroperoxides) also present in the mixture, and was obtained as a white crystalline solid upon removing the solvent at 12 mmHg from appropriate fractions.

Details for the individual compounds are given below except for m.p. and analytical data which appear in Table 1. The yields quoted below are of materials isolated from column chromatography, but unlike those given in Table 1 are based on conversions from 2,3-dibromocycloalkyl hydroperoxide.

(a) cis-7-*Bromo*-2,3-*dioxabicyclo*[2.2.1]*heptane* (12a). Ratio (10a) : (11a) (yield of 12a): 3 : 1 (16%); 1 : 3 (14%); 0 : 1 (10%). ^{1}H N.m.r. (100 MHz) δ 1.74—2.17 (AA'BB' m, 5- and 6-CH_2), 4.54 (s, CHOO), and 4.58 (s, CHBr); ^{13}C n.m.r. δ ($CDCl_3$) 82.36 (COO), 55.12 (CBr), and 27.85 p.p.m.; mass spectrum: equally intense molecular ions at *m/z* 178 and 180; base peak at *m/z* 83; i.r. $\nu_{max.}$ 2 980, 2 940, 2 850, 1 455, 1 435, 1 305, 1 290, 1 230, 1 200, 1 190, 1 175, 1 150, 1 120, 1 010, 970, 950, 910, 885, and 845 cm^{-1}.

Bromo-trifluoroacetoxy-cyclopentyl hydroperoxides were isolated in 40% yield; ^{1}H n.m.r. (60 MHz) δ 1.65—2.8 (m, 4 H), 4.50 (m, 1 H), 4.70 (m, 1 H), 5.45 (m, 1 H), and 9.0 br (s, OH); ^{13}C n.m.r. δ 91.82, 84.99, 50.49, 28.78, and 26.90 p.p.m.; and 84.26, 83.98, 53.16, 27.05, and 25.10 p.p.m.; i.r. ν_{OH} 3 605 and 3 560 cm^{-1}; $\nu_{C=O}$ 1 815 cm^{-1}.

(b) cis-8-*Bromo*-6,7-*dioxabicyclo*[3.2.1]*octane* (12b). Ratio (10b) : (11b) (yield of 12b): 1 : 0 (60%); 0 : 1, but containing 20% of (13b) (15%); ^{1}H n.m.r. (100 MHz) δ 1.46—1.94 (m, 6 H), 4.70 (d, *J* 4 Hz, CHOO), and 4.72 (s, CHBr); ^{13}C n.m.r. δ 82.89 (COO), 60.39 (CBr), 32.07, and 16.06 p.p.m.; mass spectrum: equally intense molecular ions at *m/z* 192 and 194; base peak at *m/z* 41; i.r. $\nu_{max.}$ 2 950, 2 850, 1 455, 1 440, 1 285, 1 250, 1 230, 1 190, 1 070, 1 040, 985, 950, 895, 830, and 720 cm^{-1}.

Only a very small amount of bromo-trifluoroacetoxy-cyclohexyl hydroperoxide was obtained and it was not separately isolated.

(c) cis-9-*Bromo*-7,8-*dioxabicyclo*[4.2.1]*nonane* (12c). Ratio (10c) : (11c) (yield of 12c): 1 : 0 (54%); ^{1}H n.m.r. (100 MHz) δ 1.35—2.15 (m, 8 H), 4.80 (m, CHOO), and 4.80 (s, CHBr); ^{13}C n.m.r. δ 87.50 (COO), 57.40 (CBr), 32.57, and 22.63 p.p.m.; mass spectrum: equally intense molecular ions at *m/z* 206 and 208; base peak at *m/z* 55; i.r. $\nu_{max.}$ 2 935, 2 860, 1 445, 1 430, 1 240, 1 215, 1 205, 1 180, 1 155, 1 110, 1 035, 990, 930, 890, 835, and 715 cm^{-1}.

The bromo-trifluoroacetoxy-cycloheptyl hydroperoxide was isolated in 25% yield; ^{1}H n.m.r. (60 MHz) δ 1.5—2.3 (m, 8 H), 4.3 (m, CHOO), 4.8 (dd, *J* 6 and 2 Hz, CHBr), 5.45 (m, CHO_2CCF_3), and 9.05 br (s, OH); ^{13}C n.m.r. δ 83.08, 80.57, 54.05. 30.26, 27.65, 23.57, and 21.67 p.p.m.; i.r. ν_{OH} 3 540 cm^{-1}; $\nu_{C=O}$ 1 780 cm^{-1}.

(d) cis-10-*Bromo*-8,9-*dioxabicyclo*[5.2.1]*decane* (12d). Ratio (10d) : (11d) (yield of 12d): 3 : 1, but containing 30% of dibromocyclo-octanol (40%); 0 : 1 (9%); ^{1}H n.m.r. (100 MHz) δ 1.65—2.30 (m, 10 H), 4.72 (m, CHOO), and 4.82 (t, *J* 1.75 Hz, CHBr); ^{13}C n.m.r. δ 88.59 (COO), 62.04 (CBr), 32.38, 25.82, and 25.31 p.p.m.; mass spectrum: equally intense molecular ions at *m/z* 220 and 222; base peak at *m/z* 41; i.r. $\nu_{max.}$ 2 920, 2 860, 1 460, 1 450, 1 440, 1 430, 1 315, 1 295, 1 235, 1 230, 1 190, 1 085, 1 000, 985, 955, 900, 870, 855, and 710 cm^{-1}.

Bromo-trifluoroacetoxy-cyclo-octyl hydroperoxide was obtained in about 15% yield but it was not separately isolated.

Compounds (12a) and (12d) were prepared in better yield (see Table 1) by stirring a mixture of 2,3-dibromocycloalkyl hydroperoxide (10 mmol) and silver oxide (10 mmol) in dichloromethane (50 cm^3) for 65—70 h in the dark. The isolation procedure was unchanged.

Methoxybromination of Cycloalk-2-enyl Hydroperoxides.—(*a*) *N*-Bromosuccinimide (10 mmol) was added to a stirred solution of cyclopent-2-enyl hydroperoxide (10 mmol) in dry methanol (75 cm^3) at 0 °C. Stirring was continued for 2 h during which time the mixture was allowed to come to room temperature. The methanol was removed at 12 mmHg and the residue treated with carbon tetrachloride (15 cm^3). Filtration and removal of the solvent from the filtrate at 12 mmHg afforded a mixture of bromo-methoxy-cyclopentyl hydroperoxides in the ratio 1.4 : 1 as determined by ^{13}C n.m.r. spectroscopy; δ, major isomer: 87.55, 84.85, 57.36, 55.01, 27.07, and 24.97 p.p.m.; minor isomer: 92.36, 89.22, 57.36, 52.39, 29.06, and 26.96 p.p.m.; ^{1}H n.m.r. (60 MHz) δ 1.4—2.7 (m, 4 H), 3.35 (s, OMe), 3.40 (s, OMe), 4.0 (m, C*H*OMe), 4.2—4.8 (m. CHOO and CHBr), and 9.35 br (s, OH).

(b) A similar reaction with cyclohex-2-enyl hydroperoxide afforded essentially a single bromo-methoxy-cyclohexyl hydroperoxide; ^{13}C n.m.r. δ 80.46, 80.29, 57.08, 52.72, 24.92, 24.86, and 18.60 p.p.m.; ^{1}H n.m.r. (60 MHz) δ 1.3—2.6 (m, 6 H), 3.4 (s, OMe), 3.7 (m, C*H*OMe), 3.8—4.4 (m, CHOO), 4.7 (t, CHBr), and 9.7 br (s, OH).

Peroxybromination of Cyclohex-2-enyl Bromide.—Cyclohex-2-enyl bromide was prepared from cyclohexene and *N*-bromosuccinimide in carbon tetrachloride following the published procedure.[16]

Hydrogen peroxide (4 cm^3 of 87%; **CAUTION!**) was added to a stirred mixture of cyclohex-2-enyl bromide (11.75 mmol) and *N*-bromosuccinimide (11.75 mmol) in ether (40 cm^3) at 0 °C, and stirring was continued for 45 min. The resultant clear red-brown solution was shaken with

water (200 cm^3) and the layers separated. The aqueous layer was extracted with more ether (40 cm^3). The ether layers were combined, washed with saturated sodium hydrogencarbonate solution (50 cm^3) and then water (5 × 50 cm^3), and dried ($MgSO_4$), and the solvent was removed at 12 mmHg to give the crude product.

Column chromatography afforded, in order of elution (13b) (500 mg), (13b) + (11b) (ratio undetermined; 380 mg), and (13b) + (11b) (ratio 1 : 9; 355 mg); (10b) was absent; combined yield 38%; (13b): ^1H n.m.r. (60 MHz) δ 1.5—2.6 (m, 6 H), 4.3—4.85 (m, 3 H), and 8.7 br (s, O*H*); ^{13}C n.m.r. see Table 2; i.r. ν_{OH} 3 540 and 3 480 cm^{-1}.

Reduction of Bromocycloalkyl Hydroperoxides.—(a) Triphenylphosphine (14.0 mmol) was added during 5 min to a stirred solution of 2,3-dibromocyclopentyl hydroperoxide [14.0 mmol; ratio (10a) : (11a) 2 : 1] in ether (50 cm^3) at 0 °C. The solution was stirred for 30 min at room temperature and the solvent removed at 12 mmHg. The residue was taken up in dichloromethane and the triphenylphosphine oxide removed by chromatography on silica (15 g) to afford a quantitative yield of 2,3-dibromocyclopentanol [ratio (14a) : (15a) 2 : 1]; ^1H n.m.r. (60 MHz) δ 1.7—3.0 (m, 4 H), 3.95 (s, OH), and 4.3—4.8 (m, 3 H); ^{13}C n.m.r. δ (14a): 72.41, 64.66, 52.23, 32.44, and 29.58 p.p.m.; (15a) 80.08, 61.67, 53.15, 33.59, and 31.72 p.p.m.

(*b*) A mixture of bromo-methoxy-cyclopentyl hydroperoxides (see earlier) similarly gave the corresponding alcohols; ^1H n.m.r. (60 MHz) δ 1.3—2.5 (m, 4 H), 3.2 br (s, OH), 3.40 (s, OMe), 3.42 (s, OMe), 3.6—4.4 (m, 3 H); ^{13}C n.m.r. δ, major isomer: 86.92, 72.64, 60.69, 57.67, 29.14, and 27.30 p.p.m.; minor isomer: 88.03, 79.22, 57.50, 57.24, 30.59, and 28.19 p.p.m.

(*c*) Compound (10b) similarly gave *cis*-2,*trans*-3-dibromocyclohexanol, m.p. 58—59 °C (from hexane–CH_2Cl_2; lit.,[11] 59—60 °C); ^1H n.m.r. spectrum in agreement with that published previously.[11]

(*d*) Compound (13b) similarly gave *trans*-2,*trans*-3-dibromocyclohexanol, m.p. 65—66 °C.

Epoxidation of 2,3-Dibromocyclopentanol.—A mixture of (14a) and (15a) (14 mmol; ratio 2 : 1, prepared as described above) and powdered potassium hydroxide (21 mmol) in ether (40 cm^3) was stirred for 1 h at 0 °C. Water (40 cm^3) was added, the layers were separated, and the aqueous layer was extracted with more ether (2 × 20 cm^3). The ether layers were combined and dried ($MgSO_4$), and the solvent was removed at 12 mmHg to give the crude product. Column chromatography afforded, in order of elution, *cis*-3-bromo-1,2-epoxycyclopentane (16) (536 mg, 23%) and (14a) (942 mg, 26%), identified by ^{13}C n.m.r. spectroscopy; no (15a) was recovered. Cyclopent-2-enone (14%) was detected (^1H n.m.r.) in the crude product but was not isolated by chromatography. For (16): ^1H n.m.r. (60 MHz) δ 1.5—2.4 (m, 4 H), 3.48 (s, CHO), and 4.15 (m, CHBr); ^{13}C n.m.r. δ 59.48 (CO), 58.49 (CO), 48.43 (CBr), 29.58, and 27.44 p.p.m.; i.r. $\nu_{max.}$ 3 040, 3 005, and 850 cm^{-1}.

Further treatment of the recovered (14a) with potassum hydroxide at room temperature gave no epoxide but a 2 : 1 mixture of (14a) and cyclopent-2-enone in 80% yield.

Epoxidation of Bromo-methoxy-cyclopentanols.—A mixture of two bromo-methoxy-cyclopentanols (975 mg; ratio 1.4 : 1, prepared as described above) and potassium hydroxide (6 mmol) in methanol (20 cm^3) was stirred for 3 h. The solution was diluted with water (80 cm^3) and extracted with dichloromethane (4 × 25 cm^3). The organic layers were combined and dried ($MgSO_4$), and the solvent was removed at 12 mmHg to give the crude product. Column chromatography (75% CH_2Cl_2–Et_2O as eluant) afforded, in order of elution, (i) a mixture (45 mg) containing *cis*-3-methoxy-1,2-epoxycyclopentane, cyclopent-2-enone, and the major bromo-methoxy-cyclopentanol [characterised by δ (^{13}C–O) 86.92 p.p.m.], (ii) a mixture (300 mg) containing the same epoxide and alcohol, and (iii) the same alcohol (125 mg); none of the minor bromo-methoxy-cyclopentanol [characterised by δ(^{13}C–O) 88.03 p.p.m.] was recovered. For *cis*-3-methoxy-1,2-epoxycyclopentane: ^{13}C n.m.r. δ 81.69 (COMe), 57.22 (CO), 55.75 (CO), 55.13 (OMe), 25.49, and 23.35 p.p.m.

Further treatment of the recovered alcohol with potassium hydroxide gave no epoxide and some cyclopent-2-enone.

Reaction of cis-8-*Bromo*-6,7-*dioxabicyclo*[3.2.1]*octane* (12b) *with Butyl-lithium.*—Normal precautions to exclude moisture were observed. A solution of butyl-lithium (2M; 1.1 cm^3) in hexane was added to a solution of (12b) (2 mmol) in ether (25 cm^3) cooled at −78 °C. The mixture was stirred for 10 min and then allowed to reach room temperature. Acetic acid (3 mmol) was added, the mixture filtered, and the solvent removed from the filtrate at 12 mmHg to afford a quantitative yield of *cis*-2-bromo-*cis*-3-butoxycyclohexanol (18); ^1H n.m.r. (60 MHz) δ 0.75—2.0 (m, 15 H), 2.55 br (s, OH), 3.15—3.75 (m, 4 H), and 4.55 (t, $W_{\frac{1}{2}}$ 6 Hz, CHBr); ^{13}C n.m.r. δ 78.28, 70.63, 68.95, 62.38, 31.91, 31.27, 27.68, 19.39, 17.57, and 13.87 p.p.m.; i.r. ν_{OH} 3 520 cm^{-1}.

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