Prostaglandin Endoperoxide Model Compounds. Part 2.[1] Stereospecific Synthesis of Isomeric 5-Bromo-2,3-dioxabicyclo[2.2.1]heptanes and 2-Bromo-6,7-dioxabicyclo[3.2.1]octanes

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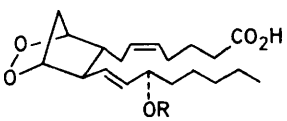
Cyclopent-3-enyl hydroperoxide (9) has been prepared from cyclopentadiene *via* hydroboration and autoxidation, and converted by bromination into *trans*-3,*cis*-4-dibromocyclopentyl hydroperoxide (10). Reaction of compound (10) with silver oxide has afforded *endo*-5-bromo-2,3-dioxabicyclo[2.2.1]heptane (11) (42%), whereas treatment of compound (10) with silver trifluoroacetate has provided *exo*-5-bromo-2,3-dioxabicyclo[2.2.1]heptane (15) (6%) and *exo*-5-trifluoroacetoxy-2,3-dioxabicyclo[2.2.1]heptane (16) (14%). The *exo*-bromide (15) (11%) has also been prepared from cyclopent-3-enyl bromide by *trans*-hydroperoxybromination and ring closure with silver oxide. The configurations of the [2.2.1]peroxides have been confirmed by catalytic hydrogenation.

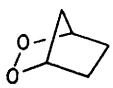
Cyclohex-3-enyl hydroperoxide (26) has been prepared from anisole by a 5-step procedure ending with oxidation of *N*-cyclohex-3-enyl-*N'*-tosylhydrazide, and converted by bromination into a mixture of two diastereoisomeric 3,4-dibromocyclohexyl hydroperoxides. Treatment of the *trans*-3,*cis*-4-dibromide (27) with silver oxide has afforded *endo*-2-bromo-6,7-dioxabicyclo[3.2.1]octane (29) (40%), whereas reaction of the *cis*-3,*trans*-4-dibromide (28) with silver trifluoroacetate has provided *exo*-2-bromo-6,7-dioxabicyclo[3.2.1]octane (30) (18%). Treatment of compound (27) with silver trifluoroacetate yielded a 9 : 1 mixture of peroxides (30) and (29) (19%), but compound (28) did not react with silver oxide.

It is suggested that the silver oxide-induced dioxabicyclizations proceed by an S_N2 mechanism whereas the silver trifluoroacetate reactions involve a bromonium ion intermediate.

SEVERAL 2,3-dioxabicyclo[2.2.1]heptanes have been prepared recently in response to the need for simple chemical models of the prostaglandin endoperoxides [*e.g.* (1)]. Two synthetic approaches have been particularly fruitful. Di-imide reduction of the singlet oxygen adducts of conjugated cycloalkadienes has provided compounds (3),[2] (4),[3] and (5),[4] in addition to the parent system (2),[5] and has been also used to prepare several homologous dioxabicyclo[*n*.2.2]alkanes (7; $n = 2$—4).[6] Reaction of 3-bromocycloalkyl hydroperoxides with silver salts has provided an alternative route to compound (2) [7] and a convenient synthesis of the 7-bromo-derivative (6),[1] together with several homologous ($n + 5$)-bromodioxabicyclo[*n*.2.1]alkanes (8) ($n = 3$—5).[1]



(1; R = OH or H)



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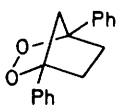

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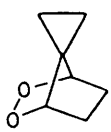

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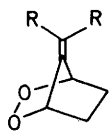
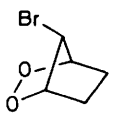


(5; R = Me or Ph)



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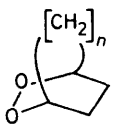

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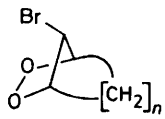


(8)

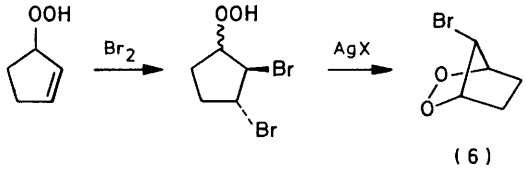
However, none of the model peroxides (2)—(6) contain substituents at the 5- or 6-positions of the [2.2.1]system as is found in the prostaglandin endoperoxides themselves. The work described in this paper was initiated with the aim of using the silver salt method to synthesize simple 5-substituted 2,3-dioxabicyclo[2.2.1]heptanes for the first time. In the course of achieving this goal, it was discovered that the dioxabicyclization of 3,4-dibromocyclopentyl hydroperoxide can be controlled, through the choice of silver salt, to yield either *exo*- or *endo* †-5-bromo-[2.2.1]peroxide stereospecifically. It has been shown that a similar effect obtains in reactions with 3,4-dibromocyclohexyl hydroperoxides and additionally that these afford [3.2.1]peroxides to the complete exclusion of the [2.2.2]isomers. Full details of these reactions are now presented.[8]

RESULTS AND DISCUSSION

[2.2.1]*Peroxides from Cyclopent-3-enyl Hydroperoxide.*—The stereospecific conversion of cyclopent-2-enyl hydroperoxide into *cis*-7-bromo-2,3-dioxabicyclo[2.2.1]-heptane (6) was achieved by treating the bromination adduct with silver oxide or silver trifluoroacetate [equation (1)].[1] It is believed that only the *cis*-2,*trans*-3-dibromide undergoes dioxabicyclization, but that isomerization in the presence of silver trifluoroacetate enables (6) to be obtained also, albeit less efficiently, from the *trans*-2,*cis*-3-dibromide. It occurred to us that bromination of cyclopent-3-enyl hydroperoxide (9) would

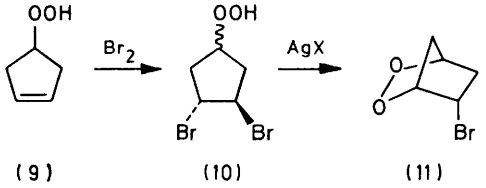
† For both [2.2.1]- and [3.2.1]-peroxides the terms *exo* and *endo* are used to describe substituents that are respectively on the opposite and same sides of the hydrocarbon ring as the peroxide bridge.

yield an adduct (10) in which *every* molecule contains a *trans*-3-bromine. It was hoped that this would lead to efficient dioxabicyclization which, by analogy with equation (1), would afford the unknown *endo*-5-bromo-2,3-dioxabicyclo[2.2.1]heptane (11) [equation (2)].



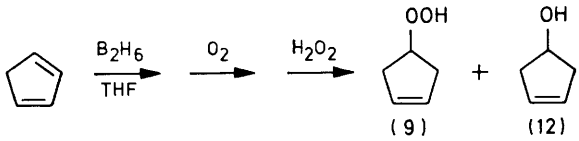
(1)

Cyclopent-3-enyl hydroperoxide has been prepared from the corresponding alcohol (12) by conversion into a methanesulphonate followed by solvolysis with basic hydrogen peroxide.[9] This classical route is not very satisfactory for secondary alkyl hydroperoxides in general, and in this case requires the initial preparation of the alcohol (12) *via* hydroboration and oxidation of



(2)

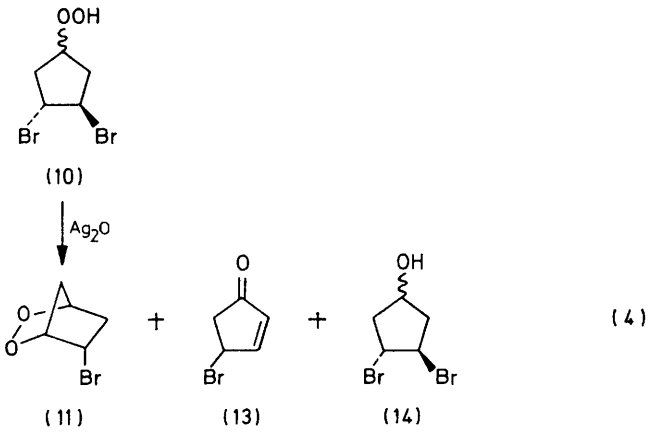
cyclopentadiene.[10] It seemed to us that hydroboration and autoxidation of cyclopentadiene might afford the desired hydroperoxide directly. Investigation of this approach led us to develop the sequence shown in equation (3), which conveniently yielded an approximately 7 : 5 mixture of compounds (9) and (12), from which the cyclopent-3-enyl hydroperoxide was readily isolated *via* its sodium salt.



(3)

Bromination proceeded smoothly in carbon tetrachloride at 0 °C and treatment of the adduct (10) with silver oxide in dichloromethane in the dark for 64 h afforded the expected *endo*-5-bromo-2,3-dioxabicyclo-[2.2.1]heptane (11) as the major product (42%). The peroxide (11) was purified by low-temperature column chromatography and the two minor products also isolated were identified as 4-bromocyclopent-2-enone (13) (6%) and 3,4-dibromocyclopentanol (14) (10%) [equation (4)].

Use of silver trifluoroacetate enabled the reaction time to be cut to 1 h, but extensive trifluoroacetate-for-bromine substitution took place and no trace of compound (11) was detected. Two bicyclic peroxides were isolated by low-temperature column chromatography, but they were identified as *exo*-5-bromo-2,3-dioxabicyclo-[2.2.1]heptane (15) (6%) and *exo*-5-trifluoroacetoxy-2,3-dioxabicyclo[2.2.1]heptane (16) (14%); the major product was a mixture of two isomers of 3-bromo-4-trifluoroacetoxycyclopentyl hydroperoxide (17) (35%) [equation (5)].



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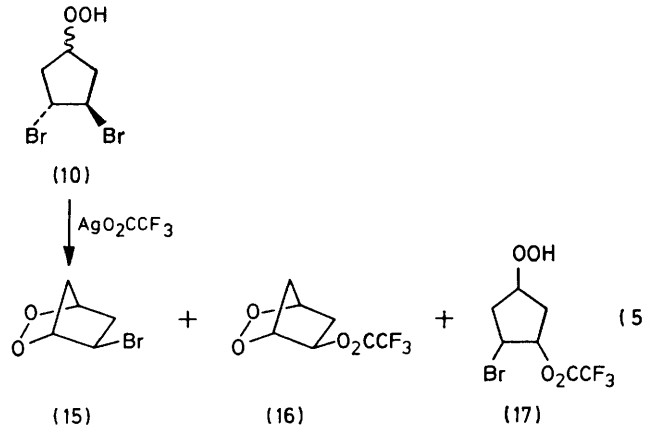
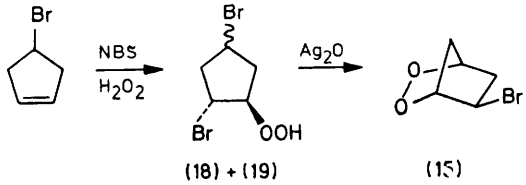


(5)

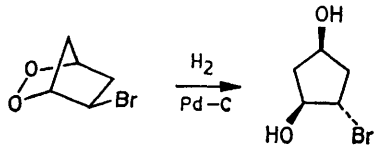
The structure of the bromo-peroxide (15) was established by an independent synthesis of it from 3-cyclopentenyl bromide *via* *trans*-hydroperoxybromination, which gave a 1 : 6 mixture of *trans*-2,*trans*-4-dibromocyclopentyl hydroperoxide (18) and the isomeric *trans*-2,*cis*-4-dibromide (19), followed by ring closure with silver oxide [equation (6)]. In fact, this represents a better route to compound (15) (11% yield) than that shown in equation (5) where ready conversion into the trifluoroacetoxy-peroxide (16) (see later) both reduces the yield and hampers the isolation of a pure sample of compound (15).



(6)

The *exo*-configuration of the bromo-peroxide (15) was confirmed by catalytic hydrogenation [equation (7)], for this afforded a 4-bromocyclopentane-1,3-diol that was identical with one of the bromohydrins (20) and (21)

obtained by reaction of cyclopent-3-enyl alcohol (12) with *N*-bromosuccinimide (NBS) and water [equation (8)]; the *trans*-nature of the hydroxybromination was confirmed by ready conversion of the bromohydrins (20)

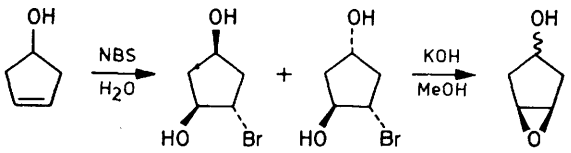


(7)

(15) (20)

and (21) into the known [11] *cis*- and *trans*-3,4-epoxycyclopentanols.

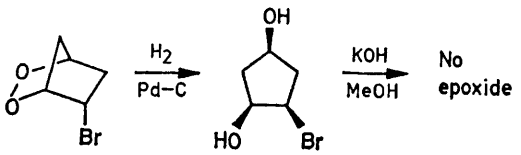
Catalytic hydrogenation also served to confirm the *endo*-configuration of the bromo-peroxide (11) and the *exo*-configuration of the trifluoroacetoxy-peroxide (16). Thus, compound (11) afforded a third 4-bromocyclo-



(8)

(12) (20) (21)

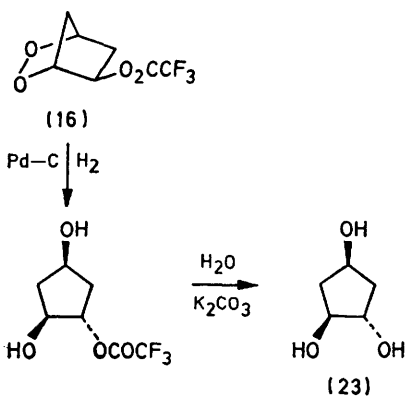
pentane-1,3-diol (22) which was shown to be a *cis*-bromohydrin by the fact that it did not epoxidize upon treatment with methanolic potassium hydroxide [equation (9)]. Catalytic hydrogenation of the peroxide (16) and subsequent hydrolysis with aqueous potassium carbonate [equation (10)] yielded a cyclopentane-1,2,4-



(9)

(11) (22)

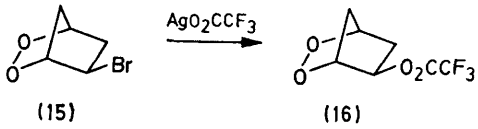
triol that had a 5-line ^{13}C n.m.r. spectrum; it was therefore assigned structure (23). The interpretation of this result as evidence for the *exo*-configuration of compound (16) depends on the reasonable assumption that the mild hydrolysis proceeded *via* configuration-preserving acyl–oxygen fission.



(10)

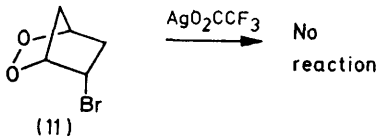
(23)

Independent experiments showed that whereas the *exo*-bromide (15) is rapidly and quantitatively converted into the trifluoroacetoxy-peroxide (16) [equation (11)], no reaction takes place between the *endo*-bromide (11) and silver trifluoroacetate [equation (12)]. The latter



(11)

(15) (16)



(12)

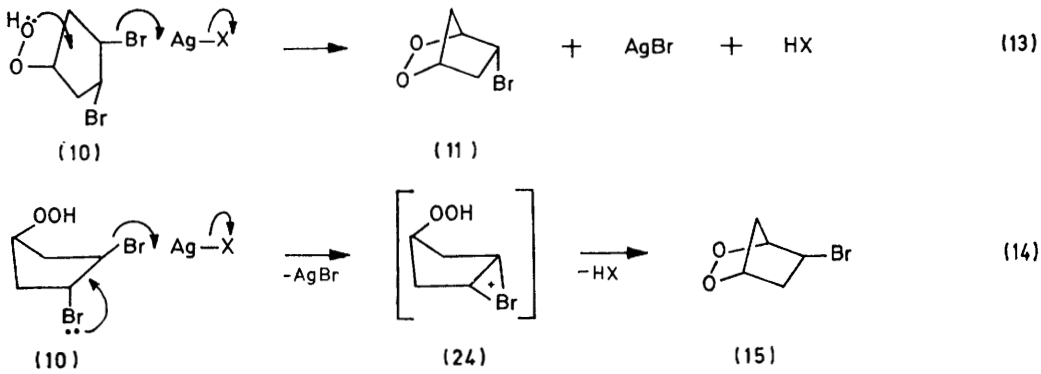
(11)

result, together with the observation that compound (11) was also inert to a mixture of silver bromide and trifluoroacetic acid, rules out the possibility that the reaction of the adduct (10) with silver trifluoroacetate [equation (5)] proceeds *via* initial formation of the expected *endo*-bromide (11) followed by transformation to the observed peroxides (15) and (16). It must be concluded, therefore, that the AgO_2CCF_3-induced dioxabicyclization of 3,4-dibromocyclopentyl hydroperoxide involves preferential displacement of the *cis*-3-bromine. It seems highly probable that this process is assisted by the vicinal bromine, *i.e.* that the *trans*-bromonium ion (24) is an intermediate. Failure to observe the analogous mechanism with 2,3-dibromocyclopentyl hydroperoxide [1] presumably reflects the disfavoured nature of the mode of ring closure needed in the corresponding species (25).

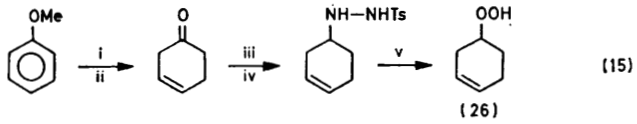
(24) (25)

Thus our results indicate that the dioxabicyclization of 3,4-dibromocyclopentyl hydroperoxide (10) may proceed either by the S_N2-type of mechanism [equation (13)] previously suggested for similar reactions with 3-bromocyclopentyl [7] and 2,3-dibromocyclopentyl [1] hydroperoxides, or by an S_N1-type of process involving a bromonium ion intermediate [equation (14)]. Furthermore, the pathway followed, and hence the stereochemistry of the bicyclic peroxides obtained, can be controlled through the choice of silver reagent.

[3.2.1] *Peroxides from Cyclohex-3-enyl Hydroperoxide.*—To seek further evidence for a bromonium ion-mediated dioxabicyclization and to investigate the regioselectivity of ring closure, we studied the reaction of 3,4-dibromocyclohexyl hydroperoxides with silver salts. The previously unknown cyclohex-3-enyl hydroperoxide (26) was prepared from anisole by the sequence of reactions shown in equation (15). Birch reduction (i) [12] followed

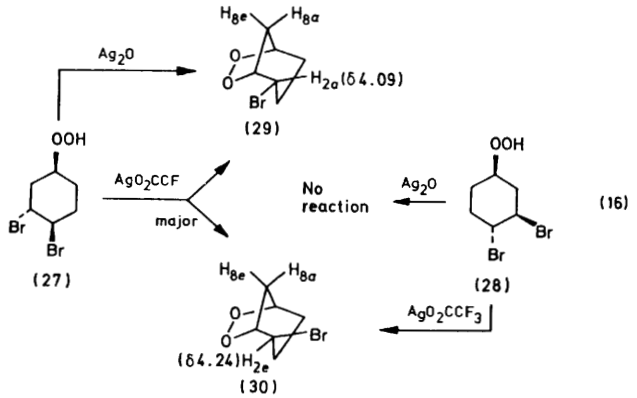


by acid hydrolysis (ii) [13] afforded cyclohex-3-enone, which was converted (iii) into the corresponding *N*-tosylhydrazone. Reduction (iv) [14] to *N*-cyclohex-3-enyl-*N'*-tosylhydrazide followed by oxidation (v) [15] then afforded the desired hydroperoxide (26).



(15)

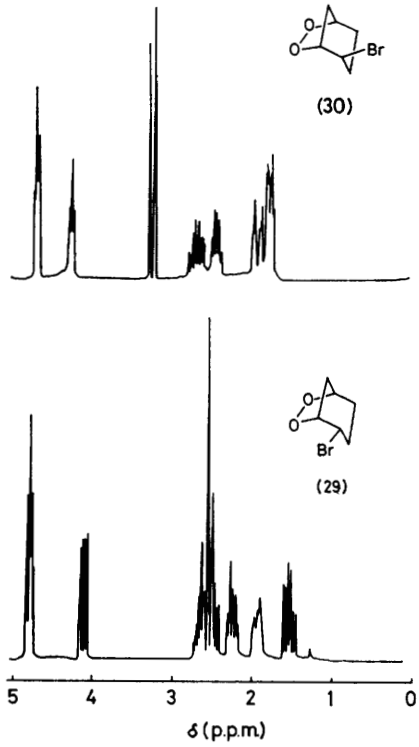
Bromination proceeded cleanly in carbon tetrachloride at 0 °C to afford a 1.8 : 1 mixture of *trans*-3,*cis*-4-dibromide (27) and *cis*-3,*trans*-4-dibromide (28); the ratio was changed to 2.6 : 1 if a silylation step [1] was incorporated. Treatment of the isomer (27) with silver oxide gave *endo*-2-bromo-6,7-dioxabicyclo[3.2.1]octane (29) (40%), whereas isomer (28) was inert [equation (16)]. However, the dibromide (28) did react with silver trifluoroacetate and gave *exo*-2-bromo-6,7-dioxabicyclo-[3.2.1]octane (30) (18%), which was separated by low-temperature column chromatography from the two isomers of bromotrifluoroacetoxycyclohexyl hydroperoxide (55%) that constituted the major product.



(16)

Treatment of isomer (27) with silver trifluoroacetate afforded a 9 : 1 mixture of bicyclic peroxides (30) and (29) in 19% yield. No evidence was found for the formation of [2.2.2]peroxides in any of the reactions [equation (16)].

The structures of compounds (27)—(30) were determined from their 200 MHz ^{1}H n.m.r. spectra, extensive decoupling experiments being used to aid the assignment of signals for the bicyclic peroxides (29) and (30). The presence of the [3.2.1]skeleton in compounds (29) and (30) was shown unambiguously by the fact that each spectrum contained a sharp doublet which was assigned to the C-8 proton (H_{8a}) *trans* to the peroxide bridge forming the A part of an ABX_2 system in which $J_{AX} = 0$. No proton in a [2.2.2]system can be envisaged to have



only one coupling. The orientation of the 2-bromine was identified from the chemical shift and coupling pattern for its geminal proton (H_{2a} or H_{2e}). The chemical shifts, which are given in equation (16), indicated the assigned stereochemistries since in cyclohexane rings equatorial protons usually appear at lower field than their axial counterparts. The assignments were confirmed by a first-order analysis of the coupling data. In the peroxide (29) the 2-proton (H_{2a}) showed one large (11.62 Hz) and one small (5.90 Hz) coupling

with the neighbouring CH_2 group and no coupling to the bridgehead proton, while in compound (30) small couplings were observed for H_{2e} with the bridgehead proton (J 5.3 Hz), with one of the protons (H_{3a}) of the neighbouring CH_2 group (J 4.0 Hz), and with the C-8 proton (H_{8e}) *cis* to the peroxide bridge (J 1.2 Hz; W-plan). These results are in accord with the structures given and the Karplus relationship.

The conversion of *trans*-3-bromide (27) into the *endo*-isomer (29) is the outcome expected for dioxabicyclization proceeding by an S_N2 mechanism [analogous to equation (13)], while formation of the *exo*-isomer (30) from either *cis*-4-bromide (27) or *cis*-3-bromide (28) is consistent with a bromonium ion mechanism [analogous to equation (14)]. Thus, the results from 3,4-dibromocyclohexyl hydroperoxides (27) and (28) [equation (16)] corroborate the conclusion from experiments with 3,4-dibromocyclopentyl hydroperoxide (10) that the silver oxide-induced dioxabicyclization proceeds by an S_N2 mechanism, whereas use of silver trifluoroacetate promotes the bromonium ion pathway. Formation of some of the *endo*-isomer (29) in the reaction of the dibromide (27) with silver trifluoroacetate indicates that both mechanisms operate here, but that the bromonium ion route is preferred.

With the 3,4-dibromocyclohexyl hydroperoxides, both S_N2 and bromonium ion pathways afford only [3.2.1]-peroxides. It seems likely that this regiospecificity is dictated by the stereochemical preference of the cyclohexane ring for a chair conformation, since this can be retained in the [3.2.1]system, while a twisted boat arrangement is required in the [2.2.2]peroxides. Formation of the [3.2.1]peroxides to the exclusion of [2.2.2]-compounds is a preparatively valuable result in that [2.2.2]peroxides are accessible *via* singlet oxygenation and several examples are known.[16] By way of contrast, the parent 6,7-dioxabicyclo[3.2.1]octane has yet to be prepared and the only derivatives previously reported are the *cis*-8-bromide,[1] the 2,4-dibromide,[17] and, after our work was completed, the 1,5-dimethyl compound.[18]

EXPERIMENTAL

General reagents, chromatographic procedures, and spectroscopic methods were as described in Part 1;[1] 200 MHz ^{1}H n.m.r. spectra were recorded for solutions in $CDCl_3$ on a Varian XL 200 instrument, and accurate mass measurements were obtained using a VG 7070 F mass spectrometer plus Finnigan INCOS data system.

Preparation of Cyclopent-3-enyl Hydroperoxide (9).—Cyclopentadiene was freshly prepared by cracking the dimer, and solvents were dried and distilled immediately before use. Diborane, which was generated by adding $NaBH_4$ (3.8 g) in diglyme (125 cm^3) to a stirred solution of $BF_3{\cdot}Et_2O$ (40 cm^3) in diglyme (25 cm^3) during 1 h, was led with a slow stream of N_2 into a stirred solution of cyclopentadiene (40 cm^3) in THF (200 cm^3) kept at 0 °C. After the addition was complete the reaction mixture was stirred for 2 h at room temperature.

The mixture was cooled to −78 °C and O_2 was bubbled through it for 1 h and then for a further 1.5 h as the temperature was slowly raised to 0 °C. At 0 °C, 27% H_2O_2 (20 cm^3) was added and the mixture stirred for 30 min before the addition of saturated aqueous $NaHCO_3$ (300 cm^3). After having been stirred for 30 min at room temperature, the mixture was extracted with hexane (100 cm^3) and CH_2Cl_2 (4 × 75 cm^3); the combined organic extracts were dried ($MgSO_4$) and the solvent removed at reduced pressure. The residue was dissolved in CH_2Cl_2 (50 cm^3) and extracted with cold 2M-NaOH (125 cm^3); the organic layer remaining after base extraction contained cyclopent-3-enyl alcohol (12) (4.95 g).

The base extract was neutralized with 2M-H_2SO_4 at 0 °C in the presence of CH_2Cl_2 (50 cm^3); the organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 cm^3). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and the solvent removed under reduced pressure to afford an oil (7.2 g), identified by ^{1}H n.m.r. as (9);[9] δ_H (60 MHz) 9.37br (1 H, s), 5.65 (2 H, s), 4.8 (1 H, quint), 2.50 (4 H, d, J 4.5 Hz); δ_C 128.31, 84.74, 37.74.

Preparation of Cyclohex-3-enyl Hydroperoxide (26).—Cyclohex-3-enone was prepared by Birch reduction of anisole [12] followed by acid hydrolysis of the resultant mixture of enol ethers.[13] Crude cyclohex-3-enone (16.6 g) in EtOH (20 cm^3) was added to a stirred solution/suspension of tosylhydrazine (32 g) in EtOH (200 cm^3), which had been prepared hot and then cooled to room temperature. A clear solution formed and after a few minutes the hydrazone began to crystallize out. The mixture was stirred at 0 °C for 30 min after which the precipitate was filtered off, washed with a little cold EtOH, and dried *in vacuo* over P_2O_5; yield 28.5 g, m.p. 135—138 °C (decomp.). *N.B.* The yield of hydrazone was drastically reduced if the reaction mixture was heated above room temperature.

The hydrazone (6.0 g) was reduced with $NaBH_4$ (1.8 g) in MeOH–H_2O at 0 °C following Caglioti and Grasselli's procedure,[14] and the resultant hydrazide was isolated by precipitation upon addition of an equal volume of water. The hydrazide was then oxidized with Na_2O_2 (2.62 g), and 27% H_2O_2 (110 cm^3) in THF (200 cm^3) in a modified version of the published procedure.[15] Column chromatography of the crude product (50%) afforded an oil (35%) which contained 90% of (26) and 10% of cyclohexyl hydroperoxide (δ_C 83.21, 30.24, 25.88, and 23.83).

This material was used for bromination (below), but an analytical sample of compound (26) was obtained *via* base extraction and careful trap-to-trap distillation; δ_H (60 MHz) 9.00br (1 H, s), 5.6br (2 H, s), 4.2 (1 H, m), 2.7—1.2 (6 H, m); δ_C 126.96, 123.74, 80.28, 29,35, 26.02, and 23.39; ν_{OH} 3 610 and 3 380 cm^{-1} (Found: C, 62.65; H, 8.9. $C_6H_{10}O_2$ requires C, 63.13; H, 8.83%).

Preparation of 3,4-Dibromocyclopentyl Hydroperoxide (10).—Bromine (10 mmol) in CCl_4 (10 cm^3) was added dropwise during 15 min to a stirred solution of cyclopent-3-enyl hydroperoxide (10 mmol) in CCl_4 (60 cm^3) at 0 °C. Removal of the solvent under reduced pressure then afforded crude compound (10) (*ca.* 95%). Usually this material was used for dioxabicyclization (below), but by column chromatography an analytical sample of compound (10) (64%) was obtained as an oil which solidified upon storage at −20 °C, m.p. *ca.* 28 °C; δ_H (200 MHz) 8.92br (1 H, s), 4.84 (1 H, m), 4.50 (1 H, m), 4.38 (1 H, m), 2.90 (1 H, m), 2.69 (1 H, m), 2.44 (1 H, m), 2.28 (1 H, d, J 10 Hz); δ_C 84.36, 54.39, 52.78, 40.04, and 39.18; ν_{OH} 3 530 and 3 400 cm^{-1} (Found: C, 23.45; H, 3.15; Br, 61.5. $C_5H_8Br_2O_2$ requires C, 23.10; H, 3.10; Br, 61.48%).

Preparation of the 3,4-*Dibromocyclohexyl Hydroperoxides* (27) *and* (28).—Bromination of cyclohex-3-enyl hydroperoxide was carried out as in the preparation of compound (10) and afforded a 1.8 : 1 mixture of compounds (27) and (28). If a silylation step was incorporated,[1] the ratio of (27) to (28) changed to 2.6 : 1. Column chromatography gave initially pure compound (27) followed by mixtures (total yield 70%); pure compound (28) was obtained *via* chromatography of the hydroperoxide mixture recovered after several reactions with Ag_2O (below). For (27): δ_H (200 MHz) 8.78 (1 H, s) 4.61 (1 H, dd, *J* 4, 4.6 Hz), 4.47 (1 H, dd, *J* 4, 4.4 Hz) overlapping with 4.41 (1 H, m) 2.62—2.4 (2 H, m), 2.3 (1 H, dt, *J* 14.2, 4.5 Hz), 2.19—2.05 (1 H, m), and 2.0—1.9 (2 H, m); δ_C 79.06, 52.96, 51.94, 34.27, 28.77, and 25.62; ν_{OH} 3 515 and 3 390 cm^{-1}. For (28): δ_H (200 MHz) 8.84 (1 H, s), 4.26—4.18 (2 H, m), 4.16—4.02 (1 H, m), 2.87—2.77 (1 H, dm, ^2J 14 Hz), 2.60—2.48 (1 H, m), 2.21—2.05 (2 H, m), 1.92—1.83 (1 H, m), 1.66—1.53 (1 H, m); δ_C 79.78, 55.04, 51.49, 37.92, 31.13, and 27.84; ν_{OH} 3 515 and 3 390 cm^{-1}. For (27) + (28), Found: C, 25.75; H, 3.6. $C_6H_{10}Br_2O_2$ requires C, 26.30; H, 3.69%.

Preparation of the trans-2,4-*Dibromocyclopentyl Hydroperoxides* (18) *and* (19).—Crude cyclopent-3-enyl bromide (1.72 g), which was prepared from reaction of PBr_3 with the crude alcohol (above) as described previously,[19] was dissolved in ether (40 cm^3) and cooled to 0 °C. Using a glass pipette, 85% H_2O_2 (1.5 cm^3) was added CAUTIOUSLY to the stirred solution, followed by *N*-bromosuccinimide (2.1 g), whereupon the mixture turned brown. After being stirred for 1 h at 0 °C a clear solution was obtained to which water (100 cm^3) was added. The ether layer was separated, washed with water (4 × 50 cm^3), dried ($MgSO_4$), and the solvent removed at 12 mmHg. The resultant oil was purified by column chromatography which afforded a mixture of compounds (18) and (19) [30%; ratio 1 : 6; (19) was assigned the *cis*-4-bromide configuration mainly because it was recovered after reaction with Ag_2O]. For (19): δ_H (60 MHz) 8.95 (1 H, s), 4.9—4.2 (3 H, m), 3.0 (1 H, dd, *J* 7, 15 Hz), 2.85—2.55 (2 H, *ca.* 2 d, *J* 4 Hz), and 2.3—1.75 (1 H, dm); δ_C 92.21, 49.89, 45.57, 43.34, and 39.51; ν_{OH} 3 500 and 3 405 cm^{-1}. For (18): δ_C 92.85, 46.39, 46.06, 42.70, and 40.26. For (18) + (19), Found: C, 23.7; H, 3.15. $C_5H_8Br_2O_2$ requires C, 23.10; H, 3.10%.

Dioxabicyclization using Silver Oxide.—An equimolar mixture of dibromocycloalkyl hydroperoxide and Ag_2O in CH_2Cl_2 (40 cm^3) was stirred vigorously for 64—72 h in the dark. The silver salts were filtered off using a glass sinter covered with a layer of Kieselguhr, and the filtrate was concentrated at 12 mmHg; the crude product was chromatographed immediately at *ca.* −15 °C. The scale, and the products isolated, which are given in the order they were eluted from the column, are reported below for the individual reactions.

(a) *With* 3,4-*dibromocyclopentyl hydroperoxide* (10) (9 *mmol*). (i) endo-5-*Bromo*-2,3-*dioxabicyclo*[2.2.1]*heptane* (11) (42%), an oil which crystallised when stored at −20 °C. An analytical sample was obtained by trap-to-trap distillation; δ_H (200 MHz) * 4.70 (s, 1-, 4-H), 4.25 (dd, $J_{5x,6n}$ 3.9, $J_{5x,6x}$ 10.5 Hz, 5x-H), 2.49 (d, $J_{6x,6n}$ 14.1 Hz, 6x-H), 2.38br (s, 7s-H, 7a-H), 2.09 (dm, 6n-H); δ_C 81.24 (C-4), 78.74 (C-1), 47.13 (off res. d, C-5), 43.67, and 40.74; $\nu_{max.}$ 2 975, 2 950, 2 925, 1 440, 1 425, 1 290, 1 270, 1 235, 1 210, 1 175, 1 150, 1 090, 1 065, 990, 945, 925, 915, 880, 700, and 650 cm^{-1}; mass spec. molecular ions *m/z* 178 (23.27%) and 180 (23.72%); base peak *m/z* 43. (Found: C, 33.84; H, 4.08; Br, 44.10%; M^+, 177.9629. $C_5H_7BrO_2$ requires C, 33.55; H, 3.94; Br, 44.64%; *M*, 177.962 99).

(ii) 4-Bromocyclopent-2-enone (13) (6%); δ_H (60 MHz) 7.7 (dd, *J* 6, 2.5 Hz, 3-H), 6.25 (dd, *J* 6, 1 Hz, 2-H), 5.2 (m, 4-H), 3.0 (A of ABX, *J* 14, 6 Hz, 5-H), and 2.7 (B of ABX, *J* 14, 2 Hz, 5-H); $\nu_{C=O}$ 1 725 cm^{-1}.

(iii) 3,4-Dibromocyclopentanol (14) (10%), identified by comparison with an authentic sample prepared by bromination of cyclopent-3-enyl alcohol (12); δ_H (60 MHz) 4.85—4.25 (3 H, m), 4.17 (1 H, s), 3.0 (1 H, m), 2.55 (2 H, m), and 2.15 (1 H, dm).

(b) *With* 2,4-*dibromocyclopentyl hydroperoxides* (18) *and* (19) (ratio 1 : 6; 5 mmol). (i) exo-5-*Bromo*-2,3-*dioxabicyclo*-[2.2.1]*heptane* (15) [11%; 77% based on (18) alone]; δ_H (100 MHz) 4.84 (m, 4-H), 4.76 (m, 1-H), 4.17 (dm, 5n-H), 2.75 (A of AB $J_{7a,7s}$ 11.5, 7a-H), 2.66 (ddd, $J_{6n,6x}$ 15, $J_{6n,5n}$ 7.5, $J_{6n,7s}$ 2 Hz, 6a-H), 2.25 (*ca.* dt, *J* 11.5, 2 Hz, 7s-H), 2.08 (dm, 6n-H); δ_C 81.67 (C-4), 78.28 (C-1), 43.81 (off res. d, C-5), 42.63, and 40.66; $\nu_{max.}$ 2 980, 2 960, 2 940, 1 440, 1 425, 1 240, 1 215, 1 145, 1 040, 1 020, 960, 925, 910, 900, and 635 cm^{-1}; mass spec. molecular ions *m/z* 178 (3.68%) and 180 (3.37%); base peak *m/z* 43; (Found: C, 34.05; H, 4.15; Br, 41.5%; M^+, 177.9629. $C_5H_7BrO_2$ requires C, 33.55; H, 3.94; Br, 44.64%; *M*, 177.962 99).

(ii) Unknown, δ_H 9.60 and $\nu_{max.}$ 1 730 cm^{-1} suggest presence of aldehyde group (possibly 3-bromopentan-1,5-dial, 5%).

(iii) 2 : 1 Mixture of compound (19) and 1-bromo-3,4-epoxycyclopentane (30%). For epoxide: δ_H 3.65br (s, 3-, 4-H); δ_C 57.80 (C-3, C-4), 41.94 (C-1), 38.95 (C-2, C-5).

(c) *With* trans-3,cis-4-*dibromocyclohexyl hydroperoxide* (27) (1.39 *mmol*). (i) endo-2-*Bromo*-6,7-*dioxabicyclo*[3.2.1]*octane* (29) (40%), an oil which solidified when stored at −20°C; δ_H (200 MHz; decoupling was used to confirm assignments and assist measurement of coupling constants) † 4.77 (m, $J_{1,8e}$ 6.8, $J_{5,8e}$ 6.2, $J_{5,4e}$ 2.1 Hz, 1-, 5-H), 4.09 (dd, $J_{2a,3a}$ 11.62, $J_{2a,3e}$ 5.90 Hz, 2a-H), 2.64 (m, $J_{8e,8a}$ 11.28, $J_{8e,4e}$ 3.8 Hz, also coupled to 1 and 5, 8e-H), 2.53 (A of AB, 8a-H), 2.50 (m, $J_{3a,3e}$ 13.32, $J_{3a,4a}$ 13.47 Hz, $J_{3a,4e}$ small, also coupled to 2a, 3a-H), 2.33 (ddd, $J_{3e,4a}$ 5.8 Hz, also coupled to 2a and 3a, 3e-H), 1.92 (m, $J_{4e,4a}$ 13.47, also coupled to 5, 8e, and 3a, 4e-H), 1.52 (dt, coupled to 3a, 3e, and 4e, 4a-H); δ_C 81.19 (C-1) 74.85 (C-5), 50.92 (off res. d, C-2), 47.11 (C-8), 31.59, and 30.02; $\nu_{max.}$ 2 920, 2 830, 1 430, 1 295, 1 270, 1 260, 1 225, 1 175, 1 155, 1 060, 1 005, 920, 910, 880, and 650 cm^{-1}; mass spec., *m/z* 192 (14.97%) and 194 (14.62%); base peak *m/z* 71 (Found: C, 37.15; H, 4.75%; M^+, 191.9787. $C_6H_9BrO_2$ requires C, 37.33; H, 4.69%; *M*, 191.978 64).

(ii) Starting compound (27) (28%).

A larger scale reaction (7.5 mmol) using a 1.8 : 1 mixture of (27) and (28) afforded (29) (24%) and starting compounds (27) and (28) (63%) in ratio 1 : 1.

Dioxabicyclization using Silver Trifluoroacetate.—The procedure adopted was similar to that used with silver oxide except that the reaction time was 1 h for 3,4-dibromocyclopentyl hydroperoxide (10) and 18 h for each of the 3,4-dibromocyclohexyl hydroperoxides (27) and (28). The scale, and the products isolated, which are given in the order

* For [2.2.1] peroxides, 5-H and 6-H are labelled x or n to indicate *exo* or *endo*, and 7-H is labelled s or a to indicate *syn* or *anti* to the O-O group.

† For [3.2.1] peroxides, protons are labelled a or e to indicate axial or equatorial w.r.t. the cyclohexane ring.

they were eluted from the column, are reported below for the individual reactions.

(a) *With* 3,4-*dibromocyclopentyl hydroperoxide* (10) (10 *mmol*). (i) *exo*-5-Bromo-2,3-dioxabicyclo[2.2.1]heptane (15) (6%).

(ii) exo-5-*Trifluoroacetoxy*-2,3-*dioxabicyclo*[2.2.1]*heptane* (16) (14%), δ_H (100 MHz) 5.12 (dm, $J_{5n,6n}$ 6 Hz, 5n-H), 4.86 (m, 4-H), 4.80 (m, 1-H), 2.48 (dm, $J_{6n,6x}$ 14 Hz, 6n-H), 2.34 (s, 7s-, 7a-H), 1.72 (dm, 6x-H); δ_C 77.45, 76.77, 74.94, 41.14, and 38.19; $\nu_{max.}$ 2 990, 2 940, 1 780, 1 445, 1 425, 1 375, 1 335, 1 220, 1 170, 1 150, 1 120, 1 055, 1 040, 1 010, 975, 960, 875, 855, 840, and 725 cm^{-1}; mass spec., *m/z* 212 (2.43%); base peak *m/z* 69 (Found: C, 39.0; H, 3.4. $C_7H_7F_3O_4$ requires C, 39.63; H, 3.32%).

(iii) Starting compound (10) (7%).

(iv) 3-Bromo-4-trifluoroacetoxycyclopentyl hydroperoxide (17) (2.2 : 1 mixture of isomers; 35%); δ_H (60 MHz) 8.5br (1 H, s), 5.4 (1 H, m), 4.75 (1 H, m), 4.35 (1 H, m), and 3.1—1.75 (4 H, m); δ_C 84.35, 83.57, 47.80, 39.51, and 34.63; and 84.48, 83.20, 46.34, 38.72, and 35.04.

(b) *With* cis-3,trans-4-*dibromocyclohexyl hydroperoxide* (28) 1.42 *mmol*). (i) exo-2-*Bromo*-6,7-*dioxabicyclo*[3.2.1]*octane* (30) (18%), an oil which solidified when stored at −20 °C; δ_H (200 MHz; decoupling was used to confirm assignments and assist measurement of coupling constants) 4.69 (*ca.* t, $J_{1,2e}$, $J_{1,8e}$, $J_{5,4e}$, $J_{5,8e}$ all *ca.* 5.3 Hz, 1-, 5-H), 4.24 (m, $J_{2e,3a}$ 4.0 $J_{2e,8e}$ 1.2 Hz, also coupled to 1, 2e-H), 3.24 (d, $J_{8a,8e}$ 11.72 Hz, 8a-H), 2.69 (m, $J_{3a,3e}$ 17.5, $J_{3a,4a}$ 13.4 $J_{3a,4e}$ 6.3 Hz, also coupled to 2e, 3a-H), 2.46 [m, coupled to 8a, 1, 5, 2e, and probably 4e (very small), 8e-H], 1.94 (dm, $J_{3e,4a}$ 3.5 Hz, also coupled to 3a and ?, 3e-H), 1.77 (m, coupled with 5, 3a, 3e, and probably 8e, 4e- and 4a-H coincident); δ_C 79.16 (C-1), 76.17 (C-5), 48.05 (off res. d, C-2), 42.77 (C-8), 27.79, and 26.99; $\nu_{max.}$ 2 920, 2 830, 1 440, 1 420, 1 320, 1 290, 1 280, 1 195, 1 180, 1 050, 1 005, 940, 890, 880, and 620 cm^{-1}; mass spec., *m/z* 192 (10.48%) and 194 (10.36%); base peak *m/z* 41 (Found: C, 36.75; H, 4.72%; M^+, 191.9785. $C_6H_9BrO_2$ requires C, 37.33; H, 4.69%; M^+, 191.978 64).

(ii) Mixture of two isomers of bromotrifluoroacetoxycyclohexyl hydroperoxide (55%); δ_H (60 MHz) 8.70br (1 H, s), 5.15 (1 H, m), 4.15 (2 H, m), and 2.8—1.2 (6 H, m); δ_C 79.37, 77.90, 49.16, 34.16, 30.84, and 28.94; and 78.49, 77.36, 49.28, 37.28, 30.02, and 25.71; ν_{OH} 3540 and 3 460 cm^{-1}; $\nu_{C=O}$ 1 785 cm^{-1}.

(c) *With* trans-3,cis-4-*dibromocyclohexyl hydroperoxide* (27) (3 *mmol*). (i) Pure *exo*-2-bromo-6,7-dioxabicyclo[3.2.1]-octane (30) (63 mg) and a mixture of *exo*- and *endo*-isomers (30) and (29) (53 mg); overall ratio 9 : 1 (19%).

(ii) Mixture of same two isomers of bromotrifluoroacetoxycyclohexyl hydroperoxide as obtained from (28) (30%).

Catalytic Hydrogenation.—(a) *endo*-5-Bromo-2,3-dioxabicyclo[2.2.1]heptane (11) (408 mg) was dissolved in EtOAc (50 cm^3) and 10% Pd–C (20 mg) was added. The flask was evacuated and filled with H_2 (× 3) and the reaction mixture was then stirred vigorously for 18 h while connected to a reservoir of H_2. The catalyst was filtered off and the solvent removed at 40 °C/12 mmHg to yield *cis*-3-bromo, *cis*-4-hydroxycyclopentanol (22) (95%); δ_H (60 MHz; $CDCl_3$) 4.65—4.0 (3 H, m), 3.4br (2 H, s), and 3.0—1.9 (4 H, m); δ_C 73.89, 70.97, 54.14, 43.44, and 40.89. No epoxide was obtained upon treatment with methanolic KOH.

(b) *exo*-5-Bromo-2,3-dioxabicyclo[2.2.1]heptane (15) (75 mg) similarly gave, after 2 h, *trans*-3-*bromo*-*cis*-4-hydroxycyclopentanol (20) (95%); δ_H (60 MHz; $CDCl_3$) 4.9—4.2 (3 H, m), 3.2br (2 H, s), 2.7—2.3 (3 H, m), and 1.8 (1 H, m); δ_C 80.72, 72.39, 53.86, 45.46, and 40.87.

(c) *exo*-5-Trifluoroacetoxy-2,3-dioxabicyclo[2.2.1]heptane (16) (90 mg) was similarly hydrogenated (4 h). The product was dissolved in water (10 cm^3), K_2CO_3 (50 mg) added, and the mixture stirred for 18 h. Removal of the solvent at 50 °C/12 mmHg afforded *trans*-3,*cis*-4-dihydroxycyclopentanol (23); δ_H (60 MHz; D_2O) 5.0 (3 H, s), 4.7—4.1 (3 H, m), 3.0—2.5 (1 H, m), 2.4—2.0 (2 H, m), and 2.0—1.6 (1 H, m); δ_C (D_2O; ref. to CH_3CN) 76.44, 76.30, 68.05, 39.67, and 39.50.

Hydroxybromination of Cyclopent-3-enyl Alcohol.—*N*-Bromosuccinimide (14.2 mmol) was added to a stirred solution of cyclopent-3-enyl alcohol (14.2 mmol) in a mixture of water (10 cm^3) and dimethoxyethane (20 cm^3). After the mixture had been stirred for 3 h the solvents were removed at 50 °C/12 mmHg. The product was dissolved in a little EtOH, cooled to −20 °C and filtered to remove precipitated succinimide. Final purification by column chromatography (CH_2Cl_2–Et_2O) afforded a mixture of compound (20) and *cis*-3-*bromo*,*trans*-4-hydroxycyclopentanol (21) (42%); δ_C 80.51, 72.12, 53.90, 45.26, and 40.91; and 79.19, 70.26, 53.38, 43.90, and 41.94.

Reaction of this mixture with methanolic KOH [1] gave a mixture of the known [11] 3,4-epoxycyclopentanols (50%); δ_H (60 MHz; $CDCl_3$) 4.05 (1 H, m), 3.65 (2 H, s), 3.0br (1 H, s), and 2.1—2.0 (4 H, m); and 4.05 (1 H, m), 3.50 (2 H, s), 3.0br (1 H, s), 2.5 (2-H, dd, *J* 14, 7 Hz), and 1.65 (2 H, dd); δ_C 69.42, 57.55, and 37.70; and 68.49, 55.90, and 36.70.

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