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(3) Trialkyltin peroxides are easily prepared by reaction of trialkyltin methoxide[4] with either alkyl hydroperoxides, to produce trialkyltin alkyl peroxides,[5] or with anhydrous hydrogen peroxide[6] to produce bis(trialkyltin) peroxides.[5]
(4) D. L. Alleston and A. G. Davies, *J. Chem. Soc.*, 2050 (1962).
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(7) R. Hiatt, *Org. Peroxides*, **3**, 6 (1972).
(8) (a) T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957); (b) H. A. Brown, Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1955, 29M.
(9) Tri(*n*-butyl)tin methoxide[4] (40 mmol) is added dropwise over 3 min to 1 M anhydrous hydrogen peroxide (20 mmol) in ethyl ether[6] at 0 °C under a blanket of dry nitrogen. After stirring 2 h at 0 °C, solvent and methanol are removed at 20 mm, the last traces being removed at 0.5 mm. Bis(trialkyltin) peroxides are somewhat unstable, but bis(tri-*n*-butyltin) peroxide may be stored under nitrogen without appreciable decomposition for several weeks in anhydrous methylene chloride solution at −20 °C. *CAUTION:* all reactions involving peroxides and especially anhydrous hydrogen peroxide should be performed behind a safety shield.
(10) A short column filled with 10% Dow Corning 710 silicone on 60/80 mesh acid washed-DMCS treated Chromosorb W. Diisopropyl peroxide,[14] 3,5-dimethyl-1,2-dioxolane,[15] and 1,2-dioxane[11] were identified by spectral comparison with authentic samples. Approximately equal amounts of the cis and trans isomers of 3,5-dimethyl-1,2-dioxolane were obtained. New compounds were characterized by elemental analysis and spectra: *1,2-dioxolane* ^{1}H NMR (CCl_4) δ 3.92 (4 H, t, J = 7 Hz), 2.53 (2 H, quint, J = 7 Hz); IR (neat) 1150 (s), 1110 (s), 987 (m), 925 (m), 780 (w); mass spectrum *m/e* (rel intensity) 26 (28), 27 (48), 28 (64), 29 (100), 30 (25), 31 (39), 42 (41), 43 (47), 44 (26), 46 (20), 74 (44); *1,2-dioxepane* ^{1}H NMR (CCl_4) δ 4.00 (4 H, m), 1.80 (6 H, m); IR (neat) 1443 (s), 1360 (m), 1260 (m), 1130 (m), 1060 (s), 1000 (s), 977 (m), 918 (m), 863 (m), 791 (m); mass spectrum *m/e* (rel intensity) 27 (79), 28 (89), 29 (94), 31 (42), 39 (62), 41 (100), 42 (69), 43 (60), 44 (40), 55 (67), 56 (69), 102 (50); *1,2-dioxocane* ^{1}H NMR (CCl_4) δ 3.87 (4 H, m), 1.70 (8 H, m); IR (neat) 1445 (s), 1370 (m), 1190 (m), 1150 (m), 1105 (m), 1070 (s), 1020 (s), 1005 (s), 947 (s), 845 (w), 816 (w), 770 (w), 733 (w); mass spectrum *m/e* (rel intensity) 27 (69), 28 (63); 29 (100), 31 (57), 39 (59), 41 (95), 42 (59), 43 (51), 44 (40), 55 (68), 56 (23), 57 (51), 67 (37), 68 (35), 69 (32), 70 (45), 98 (20), 116 (27).
(11) R. Criegee and G. Muller, *Chem. Ber.*, **89**, 238 (1956).
(12) Bis(triethylgermyl) peroxide[5] is less reactive (3 h for completion) and gives diisopropyl peroxide (41%) and isopropyl ether (9%). Bis-(trimethylsilyl) peroxide[13] gives no diisopropyl peroxide even after exposure to isopropyl triflate for 1 week at 20 °C.
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(15) A. J. Bloodworth and M. E. Loveitt, *J. Chem. Soc., Chem. Commun.*, 94 (1976).
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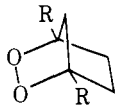
Mary F. Salomon,* Robert G. Salomon*
Department of Chemistry, Case Western Reserve University
Cleveland, Ohio 44106
Received November 15, 1976

2,3-Dioxabicyclo[2.2.1]heptane. The Strained Bicyclic Peroxide Nucleus of Prostaglandin Endoperoxides

Sir:

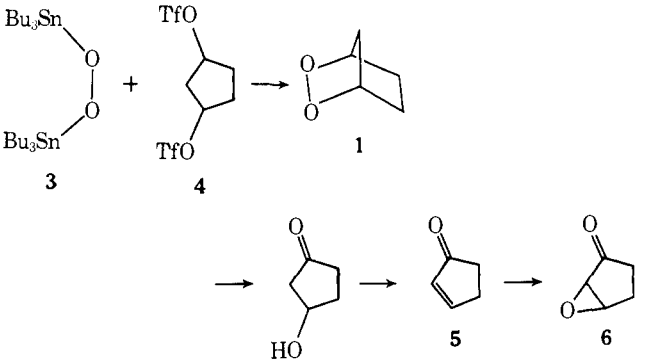
The 2,3-dioxabicyclo[2.2.1]heptane (**1**) heterobicyclic ring system assumed special importance when it was recognized as the nucleus of prostaglandin (PG) endoperoxides,[1] the pivotal immediate biological precursors of prostaglandins,[2] thromboxanes,[3] and prostacyclins.[4] We now report the first synthesis of the parent compound **1**, and record some preliminary observations on the chemical and thermal reactions of this important molecular type.



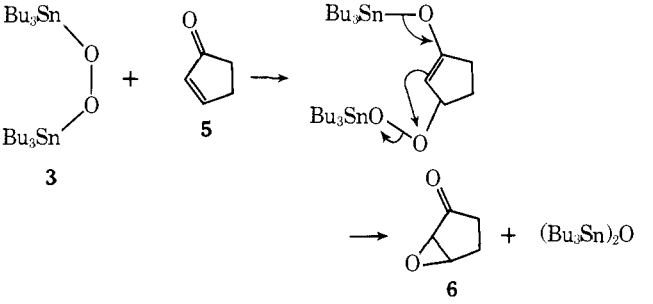
1, R = H
2, R = C_6H_5

Recently, we described the first nonenzymatic synthesis of fully characterized derivatives of **1**.[5] The bridgehead substitution in the 1,4-diphenyl derivative **2** precluded PG-endoperoxide-like reactivity involving abstraction of a bridgehead proton. The stability of **2** was found not to differ significantly from common ditertiary alkyl peroxides in contrast with the extreme thermal and chemical instability observed for PG-endoperoxides.[11] In planning a synthesis of **1**, we assumed that this bridgehead unsubstituted bis secondary alkyl peroxide would be especially sensitive toward base induced disproportionation[6] as observed for PG-endoperoxides. Our previous discovery that alkyl hydroperoxides can be alkylated in excellent yields with secondary alkyl trifluoromethane sulfonates (triflates) under mild, nonalkaline conditions,[7] led us to examine the reaction of bis(tri-*n*-butyltin) peroxide (**3**) with alkyl triflates. The successful development of an effective new synthesis of primary and secondary peroxides based on peroxide transfer from **3** to alkyl triflates was described in the accompanying communication.

A bistriflate **4** was prepared from *cis*-1,3-cyclopentanediol as described previously.[7] An exothermic reaction occurred when **3** and **4** were combined in a 1:1 molar ratio. No trace of **1** was detected in the reaction product mixture by ^{1}H NMR. The volatile products, isolated by vacuum transfer (0.03 mm) into a cold trap (−78 °C), included variable amounts of 2-cyclopenten-1-one (**5**)[8] and 2,3-epoxycyclopentan-1-one (**6**).[9]



It seemed likely that **5** arose by disproportionation of the sensitive peroxide **1** under the reaction conditions, followed by dehydration of the resulting β-hydroxy ketone, as in the disproportionation of PG-endoperoxides to PGE and subsequent dehydration to PGA. Apparently, as expected, the rigid, strained, bicyclic peroxide **1** is unusually reactive. The α,β-unsaturated ketone **5** was shown to give **6** (40% yield) upon treatment with **3**. This novel aprotic epoxidation most likely involves initial nucleophilic 1,4-addition to eneone **5**, followed by intramolecular nucleophilic displacement of tin oxide.[10]



Since **3** is essentially nonvolatile, alkylations of **3** can be conducted in vacuo, in contrast with syntheses of peroxides based on alkylation of hydrogen peroxide. The bicyclic peroxide **1** was obtained in 13% yield, when the reaction between **3** and **4** was conducted in vacuo (0.1 mm) with transfer of the volatile products to a cold trap (−78 °C) as they were formed. Best results were achieved with 1,2,4-trichlorobenzene as re-

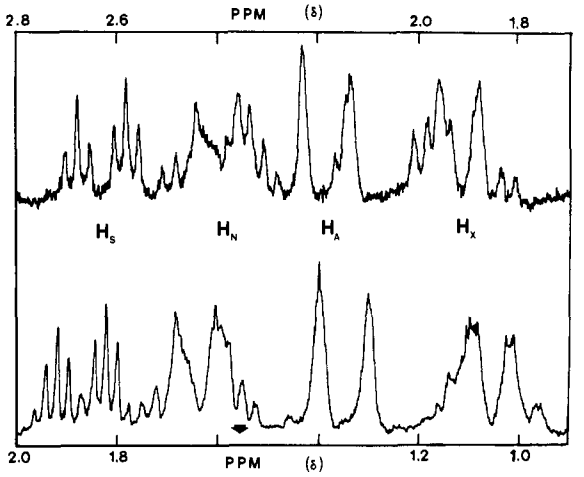
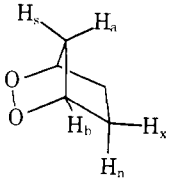
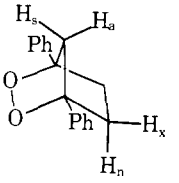


Figure 1. Upfield region of 100-MHz ^{1}H NMR spectra of **1** (bottom) and **2** (top) in C_6H_6 (note different scales).

action solvent. The peroxide was separated from other products and some trichlorobenzene by thin layer chromatography on silica gel at −20 °C with methylene chloride as developing and eluting solvent. The peroxide **1** gives a strong positive peroxide test with ferrous thiocyanate[11] which can be used for visualization on TLC plates. A solution of **1** in perdeuteriobenzene was prepared by addition of this solvent and evaporation of CH_2Cl_2 under reduced pressure. The methylene protons of **1** exhibit an almost identical ^{1}H NMR spectrum as the corresponding protons of **2** except that all resonances for **2** occur 0.8



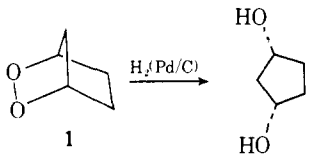
1



2

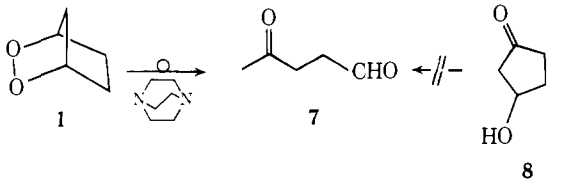
ppm downfield from the corresponding resonances for **1** (Figure 1). Thus, **1** exhibits four multiplets centered at δ 1.05, 1.35, 1.64, and 1.87 for H_x, H_a, H_n, and H_s respectively, compared with δ 1.90, 2.17, 2.40, and 2.64 for the corresponding protons of **2.** The ^{1}H NMR spectrum of **1** also exhibits a two proton broad singlet at δ 4.2 due to the bridgehead hydrogens, H_b.

After chromatographic purification, **1** is quite thermally stable. Decomposition occurs slowly upon prolonged heating (C_6D_6 solution) at 70 °C ($t_{1/2} \simeq 3$ h). Thus, 2,3-dioxabicyclo[2.2.1]heptane exhibits much greater thermal stability than might have been expected since PG-endoperoxide preparations obtained by bioconversion are much less thermally stable ($t_{1/2}$ = 2.7 h at 20 °C in light petroleum–diethyl ether 1:1).[1] Catalytic hydrogenation (Pd/C) of **1** in ethanol gives *cis*-1,3-cyclopentane diol[8] exclusively (no trace of trans diol).



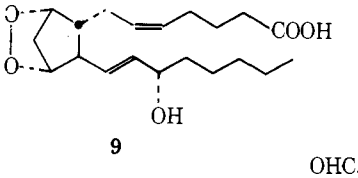
1

The peroxide **1** underwent an unexpected rearrangement upon exposure to 1,4-diazabicyclo[2.2.2]octane (20 mole % in C_6D_6). Levulinaldehyde (**7**)[8,12] was obtained in 80% yield within 20 min at 35 °C. The possibility that **7** might arise via retro-aldol cleavage of 3-hydroxycyclopentan-1-one (**8**)[13] was ruled out since **8** is inert under the rearrangement reaction conditions. Further study is needed to establish a mechanism



1 **7** **8**

for this unprecedented reaction. Moreover, prostaglandin endoperoxides (e.g., **9**) may well be susceptible to analogous rearrangement (e.g., to **10** and **11**). The biological ramifications of such transformations demand scrutiny.[14]



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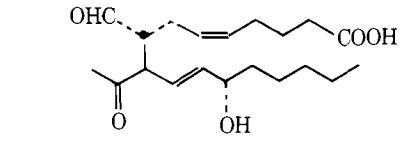

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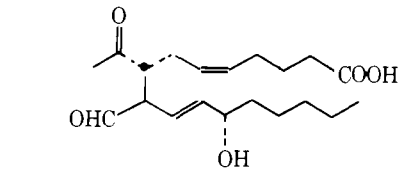
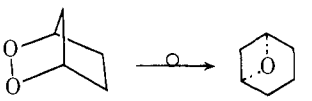


11

The synthesis of **1** reported herein may be adaptable to the synthesis of PG-endoperoxides themselves. In any event, we expect that studies on the chemistry of **1** will provide insights into the biological transformations of PG-endoperoxides. In particular, attempts to induce rearrangement of **1** to 2,6-dioxabicyclo[3.1.1]heptane (**12**), the nucleus of thromboxanes, as well as disproportionation, and fragmentation reactions are now in progress.



1 **12**

Acknowledgment. This research was supported by Grant GM-21249 from the Division of General Medical Sciences of the National Institutes of Health.

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(4) *Chem. Eng. News*, **54** (52), 17 (1976).

(5) D. J. Coughlin and R. G. Salomon, *J. Am. Chem. Soc.*, **99**, 655 (1977).

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(7) M. F. Salomon, R. G. Salomon, and R. D. Gleim, *J. Org. Chem.*, **41**, 3983 (1976).

(8) Identified by ^{1}H NMR and GLC comparison with an authentic sample.

(9) ^{1}H NMR (60 MHz, in CCl_4) δ 1.8–2.5 (4 H, m), 3.17 (1 H, d, J = 2.3 Hz), 3.81

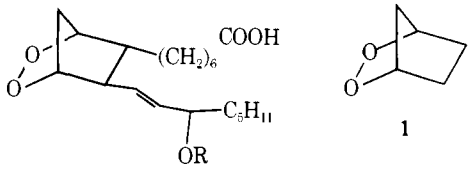
(1 H, d, J = 2.3 Hz).
(10) A similar epoxidation occurs in the reaction of α,β-unsaturated ketones with the sodium salt of *tert*-butyl hydroperoxide: N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).
(11) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, **40**, 1680 (1975).
(12) A. Mondon, *Angew. Chem.*, **64**, 224 (1952); ^{1}H NMR (60 MHz, in C_6D_6) δ 1.72 (3 H, s), 2.18 (4 H, s), 9.36 (1 H, s).
(13) J. M. McIntosh and P. Beaumier, *J. Org. Chem.*, **37**, 2905 (1972).
(14) Note Added in Proof: Imidazole catalyzes the rearrangement of 1 to a mixture of **7** and **8** (1:1).

Robert G. Salomon,* Mary F. Salomon*
Department of Chemistry, Case Western Reserve University
Cleveland, Ohio 44106
Received January 6, 1977

2,3-Dioxabicyclo[2.2.1]heptane

Sir:

The isolation of the two prostaglandin bicyclic endoperoxides PGG and PGH[1] has sparked considerable synthetic interest in the 2,3-dioxabicyclo[2.2.1]heptane structure. These endoperoxides have not only been identified as intermediates in prostaglandin formation, but they have also been shown to exhibit strong and independent physiological effects, as well.

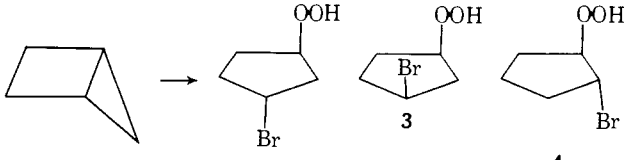


PGG, R = OH
PGH, R = H

1

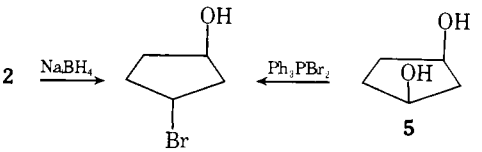
Primary or secondary dialkyl peroxides are usually prepared by the alkylation of basic hydrogen peroxide with alkylmesylates[2] or by the reaction of alkyl mesylates or halides with superoxide.[3-5] The conditions of the basic hydrogen peroxide reaction are, however, too harsh for a product endoperoxide like PGG to survive and the superoxide method has thus far failed to yield bicyclic endoperoxides. We reasoned that the conditions used for the synthesis of unstable dioxetanes[6] (β-bromohydroperoxides and silver acetate) might also be successfully employed for the synthesis of the bicyclic endoperoxide structure. We report here the successful synthesis of **1** via the reaction of silver acetate and *trans*-3-bromocyclopentane hydroperoxide.The conversion to **1** is clean and quantitative and thus provides a promising route to the prostaglandin endoperoxides.

Reaction of bicyclopentane[7] (0.027 mole) with 98% H_2O_2 (1.06 mol) and *N*-bromosuccinimide (0.03 mol) in diethyl ether at −41 °C (3 h) led to the formation of three bromohydroperoxides which could be separated by silica chromatography at −10 °C.[8] **2** and **3** were the major products formed (1:1 ratio) with **4** comprising less than 5% of the mixture. The



2 4

structures of **2** and **3** are supported by proton and carbon magnetic resonance spectroscopy,[9] iodometric titration, and reduction ($NaBH_4$) to the γ-bromocyclopentanols. *trans*-3-Bromocyclopentanol was prepared independently from *cis*-1,3-cyclopentanediol[10] by reaction with triphenylphosphine dibromide,[11] a reaction known to occur with inversion of configuration.[12] The γ-bromo alcohol derived from reduction of **2** was identical with that prepared from the diol in every respect.[13]

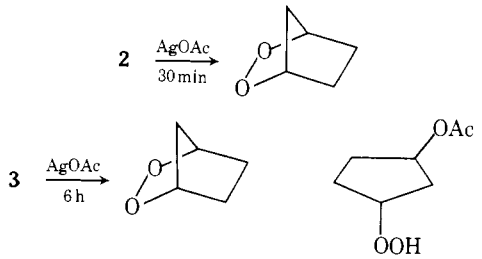


5

Reaction of **2** (3.45 mmol) in a stirred slurry (CH_2Cl_2) of silver acetate (20.5 mmol) for 30 min led quantitatively to **1** as judged by NMR. The ^{1}H NMR of this peroxide is characterized by a dominant broad singlet at δ 4.8 with the region between δ 1.6 and 2.5 being remarkably similar to that of the 2,3-diazabicyclo[2.2.1]hept-2-ene azo analogue[14] (^{1}H NMR of **1** (CCl_4) δ 1.6–2.1 (4 H, m), 2.2–2.4 (2 H, m), 4.8 (2 H, s)). The ^{13}C NMR of **1** consists of signals at 29.1, 43.8, and 78.8 ppm (reference Me_4Si), consistent with the symmetry of the molecule. **1** can be purified by bulb to bulb distillation, low temperature crystallization (pentane), or sublimation, and the white crystalline material thus purified melts at 42.0–43.5 °C dec. **1** is remarkably stable in organic solvents and a carbon tetrachloride solution of the endoperoxide has been warmed briefly to 60 °C without significant decomposition. Prolonged heating does lead to decomposition products that absorb in the carbonyl region of the infrared.

Reduction of **1** (thiourea)[15] followed by acetylation (acetic anhydride–pyridine) leads to *cis*-1,3-diacetoxycyclopentane that is identical in every respect[13] with material prepared independently from authentic *cis*-1,3-cyclopentanediol.[10]

Reaction of the *cis*-γ-bromocyclopentane hydroperoxide **3** with silver acetate occurs with a much slower rate than the reaction of **2.** Thus, after reaction of **3** with silver acetate for 4 h under conditions similar to those described for **2,** a significant amount of **3** remains. After complete consumption of **3** (6 h), **1** and a new product tentatively identified as 3-acetoxycyclopentane hydroperoxide are present in the reaction mixture.



The dramatic differences in rate and product specificity found in the reaction of **2** and **3** with silver acetate point to the involvement of the hydroperoxide group in the transition state. In particular, the hydroperoxy group appears to be assisting in the loss of bromide via an intramolecular S_N2 type transition state.

The formation of the γ-bromohydroperoxides from bicyclopentane also deserves comment. Addition of molecular bromine or chlorine to the strained bridge bond of bicyclopentane occurs with predominant formation of the trans 1,2 dihalide.[16] In the reaction reported here, hydrogen peroxide, an excellent nucleophile present in excess, presumably traps the first formed carbonium ion species before rearrangement to the stable bridged 1,2 bromonium ion can occur.

The success of the silver salt–hydroperoxide approach and the recent report[17] of organic peroxide synthesis via alkylhalides, silver salts, and hydrogen peroxide suggested that *cis*-1,3-cyclopentanedibromide,[18] **6,** might be a precursor of endoperoxide **1.** In fact, **6** can be converted to **1** in 30–40% yield by its reaction in methylene chloride with silver acetate or silver trifluoroacetate and hydrogen peroxide. Thus, 1,3 bromohy-