Decomposition of Bicyclic Endoperoxides: An Isomorphous Synthesis of Frontalin via 1,5-Dimethyl-6,7-dioxabicyclo[3.2.1]octane

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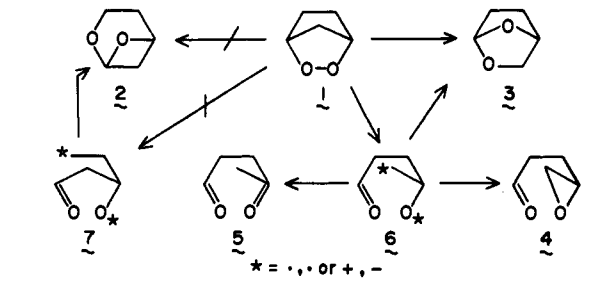
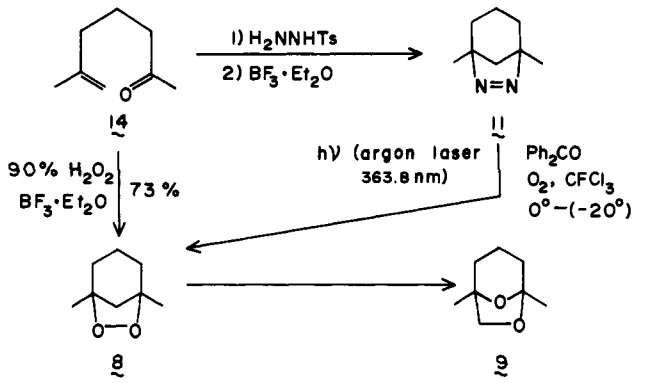
With the recognition of the central role played by the bicyclo[2.2.1] endoperoxide in the biosynthesis of the prostanoids,[1] the preparation and chemistry of bicyclic endoperoxides have become areas of intense interest.[2] Therefore we wish to report the synthesis of the first example of a bicyclo[3.2.1] endoperoxide and several important factors which influence bicyclic endoperoxide decomposition.

We have been particularly intrigued by the observation that the unsubstituted endoperoxide **1** does not rearrange to the thromboxane A_2 analogue **2** (Scheme I)[2g] as would be expected from the chemistry proposed for the prostaglandin endoperoxide.[1b,c] Instead **1** fragments to **3**, **4**, and **5**. It has been observed[2g,h] that **3** and **4** arise from a homolytic carbonyl extrusion[3] (Scheme I, **6**, * = ·,·) while **5** arises from a heterolytic extrusion (**6**, * = +,−). These three products arise from extrusions involving the one-carbon bridge (via **6**); in the unsubstituted system no products arising from extrusions involving the two-carbon bridge (**7**) have been observed.[2g,4] This dichotomy can be understood within the framework of the carbonyl extrusion model with the aid of the dihedral angle relationships shown in Figure 1. In these perspective drawings the relative dihedral angles between the peroxide bond and the two potentially labile bridge bonds are shown for the [2.2.1] and [3.2.1] endoperoxides **1** and **8**, respectively. These angles provide a measure of the overlap between the peroxide bond orbitals and the bridgehead carbon orbitals as the peroxide bond breaks.[5] In both systems, the better overlap with the one-carbon bridge should lead to its more facile rupture in a concerted carbonyl extrusion.[6] In order to test this hypothesis further, we have prepared the bicyclo[3.2.1] endoperoxide **8** and studied its transformation into the pine beetle pheromone frontalin (**9**)[7] (Scheme II).

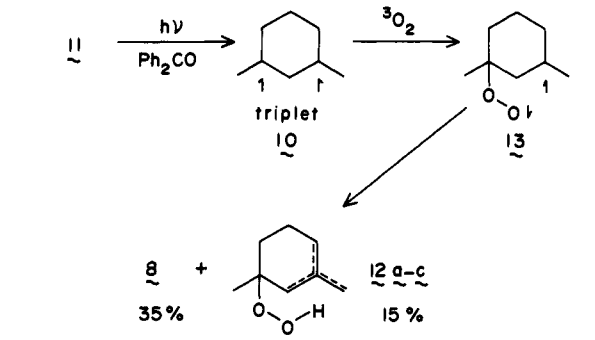
Scheme I



Scheme II



Scheme III



Scheme IV

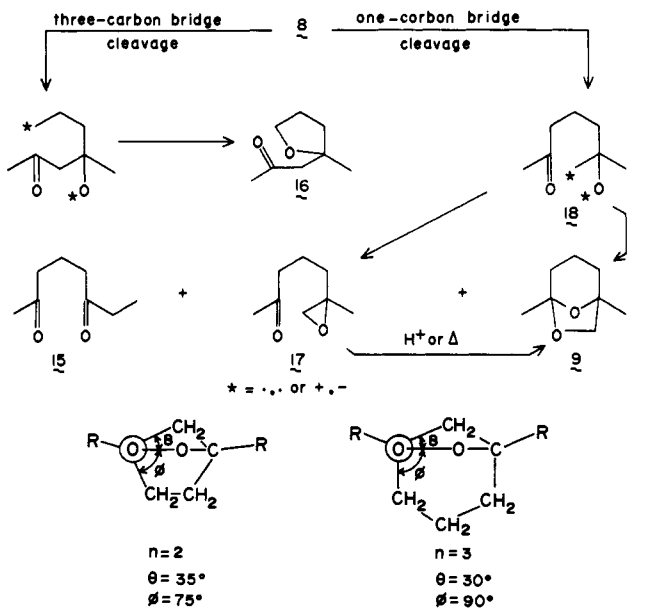


Figure 1. Dihedral angle relationship between the peroxide and the one-carbon and the *n*-carbon bridges.

Two routes to **8** have been developed (Scheme II). The initial method of preparation consisted of generating the triplet biradical

(1) (a) Samuelsson, B. *J. Am. Chem. Soc.* **1965**, *87*, 3011. (b) Gibson, K. H. *Chem. Soc. Rev.* **1977**, *6*, 489. (c) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 293.

(2) (a) Salomon, R. G.; Salomon, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 3501. (b) Porter, N. A.; Gilmore, D. W. *Ibid.* **1977**, *99*, 3503. (c) Adam, W.; Eggelte, H. J. *J. Org. Chem.* **1977**, *42*, 3987. (d) Wilson, R. M.; Geiser, F. *J. Am. Chem. Soc.* **1978**, *100*, 2225. (e) Coughlin, D. J.; Salomon, R. G. *Ibid.* **1977**, *99*, 655. (f) Adam, W.; Durán, N. *Ibid.* **1977**, *99*, 2729. (g) Salomon, R. G.; Salomon, M. F.; Coughlin, D. J. *Ibid.* **1978**, *100*, 660. (h) Porter, N. A.; Byers, J. D.; Holden, K. M.; Menzel, D. B. *Ibid.* **1979**, *101*, 4319. (i) Johnson, R. A.; Nidy, E. G.; Baczynskyj, L.; Gorman, R. R. *Ibid.* **1977**, *99*, 7738. (j) Coughlin, D. J.; Brown, R. S.; Salomon, R. G. *Ibid.* **1979**, *101*, 1533. (k) Coughlin, D. J.; Salomon, R. G. *Ibid.* **1979**, *101*, 2761.

(3) When the peroxide linkage is part of a 1,2-dioxolane ring which may be either monocyclic[2f] or part of a bicyclic ring system,[2k] peroxide decomposition proceeds by a two-bond scission (carbonyl extrusion) rather than a stepwise cleavage of first the peroxide bond and then a β carbon–carbon bond.

(4) The product distributions observed by Salomon, Salomon, and Coughlin for the 2,3-dioxabicyclo[2.2.1]heptane[2g] have been confirmed in our studies with the same material (Wilson, R. M.; Geiser, F., unpublished results) and with 1,4-dimethyl-2,3-dioxabicyclo[2.2.1]heptane (Wilson, R. M.; Rekers, J. W., unpublished results).

(5) Similar arguments have been advanced to account for α cleavage or the Norrish type I cleavage in carbonyl photochemistry: Zimmerman, H. E. *Adv. Photochem.* **1963**, *1*, 198.

(6) However, in the [2.2.1] system, two-carbon bridge cleavage might occur if the extrusion intermediate **7** (Scheme I) or the transition state leading to cleavage of the two-carbon bridge is stabilized by appropriate substituents. The fragmentation of 6-vinyl-2,3-dioxabicyclo[2.2.1]heptane to malondialdehyde and butadiene might be an example of the vinyl substituents stabilizing the fragmentation intermediate (Wilson, R. M.; Moats, D. L., unpublished results). The fragmentation of 4,4-diphenyl-2,3-dioxabicyclo-[2.2.1]heptane[2e] to dibenzoylmethane and ethylene might be an example of transition state stabilization.

(7) Kinser, G. W.; Fentiman, A. F.; Page, T. F.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature (London)* **1969**, *221*, 477.

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Table I. Decomposition of Endoperoxide 8

decomposition conditions	yields, % 9	15[a]	16	17[b]
1. thermal: 400 °C vapor phase	40	21	5	
2. photochemical: direct irradiation,[c] $CFCl_3$, −20 °C				100
3. photochemical: Ph_2CO sensitized,[c] $CFCl_3$, −20 °C	100			
4. $TiCl_4$, CH_2Cl_2, 0 °C		95		
5. $AlCl_3$, $CDCl_3$, 43 °C		45		
6. TsOH, THF, reflux	5	5	50	
7. $FeCl_3$, THF, H_2O, reflux	9	5	34	

[a] Under acidic conditions 15 undergoes aldol condensations to afford 2,3-dimethylcyclohex-2-enone and 3-ethylcyclohex-2-enone. The yields of these cyclohexenones are included in the yields of 15. [b] The epoxide 17 is readily transformed into frontalin (9) by acid or heat. Therefore it was usually impossible to determine whether 9 was a primary product or derived from 17. [c] The ultraviolet output (3 W) of an argon ion laser was used: 363.8, 351.4, 351.1, 335.8, 334.5, and 333.6 nm.

10 via photosensitized decomposition of the azoalkane **11**,[8] using monochromatic laser light, and trapping this species with oxygen under high pressure[1d] (Scheme III). In this sequence evidence for a stepwise biradical trapping has been obtained for the first time. The observation of the three possible olefinic hydroperoxides **12a–c** indicates the intermediacy of the hydroperoxy biradical **13** which can undergo either intramolecular hydrogen abstraction to form the hydroperoxides **12a–c** or closure to form the endoperoxide **8**. Unfortunately, these hydroperoxides complicate the isolation of the desired endoperoxide **8**. Therefore, we were most pleased to observe that the same ketone (**14**)[8] used in the azo route (Scheme II) could be converted directly to **8** in much higher yields via a unique acid-mediated cyclization with hydrogen peroxide.[9]

With endoperoxide **8** available in quantity,[10] it has become possible to study its decomposition under a variety of conditions (see Table I). The rapid thermal decomposition of **8** proceeds at about 400 °C in the vapor phase. Preferential one-carbon bridge cleavage is observed, with frontalin (**9**) being the major product along with diketone **15** (Scheme IV). A small amount of the three-carbon bridge cleavage product **16** is also formed thermally. Conditions have been found which lead to preferential formation of each of the products listed in Table I: **9**, **15**, **16**, and **17**. Thus, direct photodecomposition with all of the ultraviolet lines of an argon ion laser leads to the quantitative formation of the epoxide **17**.[11] In contrast benzophenone-sensitized photodecomposition leads to quantitative formation of frontalin (**9**). Lewis acid mediated decomposition of **8** leads to the exclusive formation of the diketone **15**, whereas protic acid favors cleavage of the larger bridge and formation of **16**. The structures of all decomposition products were confirmed by synthesis.[10,12]

Epoxide **17** arising from direct excitation of the peroxide could be produced via homolytic extrusion and collapse of a singlet species (Scheme IV, **18**, * = ↑,↓). The ketal **9** arising from photosensitization could be produced via a homolytic extrusion to a triplet species (Scheme IV, **18**, * = ↑,↑) from which bond rotation and stepwise addition to the carbonyl could occur before spin inversion would make possible collapse to the epoxide **17**. The formation of the diketone **15** (Scheme IV) and the keto aldehyde **5** (Scheme I) implies the intermediacy of an ionic species with a substantial amount of positive charge on the bridge carbon fragments (Scheme IV, **18**, * = +,–; Scheme I, **6**, * = +,–). Such species would be expected to undergo 1,2-methyl and -hydride shifts to form the dicarbonyl compounds observed. The formation of the three-carbon bridge cleavage product **16** might be rationalized as outlined in Scheme IV (* = +,–) but it is felt that this pathway is inconsistent with the dihedral angle considerations outlined earlier. Since this product is characteristic of decompositions in protic medium, we suspect that a basic change in mechanism has occurred to one involving the protic solvent or acid[13] and are currently investigating this point.

Finally, the route to the pine beetle pheromone frontalin (**9**) via **11** and **8** constitutes an isomorphous synthesis, since the molecular skeleton of these three substances does not change but only the locations of the heteroatoms within that molecular skeleton are altered. This isomorphism with respect to the natural pheromone frontalin (**9**) probably accounts for the strong electroantennagram signals observed when antenna of the western pine beetle *Dendroctonus brevicomis* are exposed to either the azoalkane **11** or the peroxide **8**.[14] We are continuing to investigate the role of **8** and other peroxides in natural products chemistry.

Acknowledgment. We thank the NSF for financial support (Grant No. CHE 76-15343) and M. C. Birch and D. M. Light for conducting the electroantennagram studies.

(8) Wilson, R. M.; Rekers, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 4005. Wilson, R. M.; Elder, R. C.; Packard, A. B.; Rekers, J. W. *Ibid.* **1980**, *102*, 1633.

(9) The mechanistic aspects of this unique cyclization are uncertain at present.

(10) All new compounds described here had satisfactory elemental analysis and spectral properties in accord with their proposed structures. **8**: IR (neat) 2840–3000, 1448, 1370, 1343, 1301, 1235, 1164, 1028, 854 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.30 (6 H, s), 1.5–2.0 (6 H, complex), 2.16 (2 H, br s); *m/e* 142 (M^+).

(11) The nature of the electronic transition(s) which gives rise to this process is not at all clear. Apparently there are very weak and broad bands associated with the peroxide linkage at wavelengths greater than about 333 nm. The spectroscopy of the peroxide linkage is being investigated further.

(12) Epoxidation of **14** with MCPBA under buffered conditions afforded **17** followed by conversion to frontalin (**9**) under acidic conditions. Ozonolysis of 1-methyl-2-ethylcyclopentene afforded diketone **15**. The tetrahydrofuran **16** was prepared in a multistep sequence starting with the THP derivative of 5-hydroxypentan-2-one. Horner–Emmons chain extension with the sodium salt of triethyl phosphonoacetate gives the THP derivative of ethyl 6-hydroxy-3-methyl-2-hexenoate. Saponification of this ester followed by treatment with methyllithium yields the methyl ketone which upon removal of the THP blocking group with acid yields **16**: IR (neat) 1706 cm^{-1}; NMR (60 MHz, $CDCl_3$) δ 1.24 (3 H, s), 1.75–2.05 (4 H, br m), 2.19 (3 H, s), 2.63 (2 H, s), 3.83 (2 H, br t, J = 6 Hz); *m/e* 142 (M^+).

(13) The greatly diminished stability of bicyclo[2.2.1] endoperoxides in protic solvents has been observed before: Nugteren, D. H.; Hazelhof, E. *Biochim. Biophys. Acta* **1973**, *326*, 448. Hamberg, M.; Svensson, J.; Wakabayashi, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345 and ref 2g and 2k. However, the formation of new products in the presence of protic species has not been observed until now.

(14) Electroantennagram signals of the following intensity relative to that observed for the same quantity of frontalin (**9**) were observed: azoalkane **11**, male (53–81%), female (43–105%); peroxide **8**, male (20–39%), female (62–90%). Competitive receptor-site studies indicated that **8**, **11**, frontalin (**9**), and *exo*-brevicomin all compete for the same antenna receptor sites. Light, D. M.; Birch, M. C. *J. Insect. Physiol.* **1979**, *25*, 161. Dickens, J. C.; Payne, T. L. *J. Ibid.* **1977**, *23*, 481. The biochemical and biological significance of these most intriguing findings must await further studies with the intact insects.

2,2′,5,5′-Tetramethyldistibolyl. A Thermochromic Distibine

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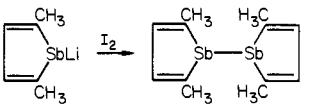
In the course of our investigation of aromatic antimony compounds[1] we have found that lithium 2,5-dimethylstibacyclopentadienide (**1**) will undergo coupling on treatment with iodine to give 2,2′,5,5′-tetramethyldistibolyl (**2**).



1 **2**

(1) Ashe, A. J., III; Diephouse, T. R. *J. Organomet. Chem.*, in press.

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