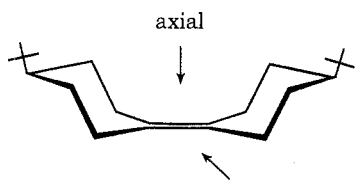
Reaction of Singlet Oxygen with Conformationally Fixed Cyclohexylidenecyclohexanes. Failure of an All Suprafacial Mechanism

Summary: Conformationally fixed C_{2v} and C_{2h} conformers of cyclohexylidenecyclohexane react with singlet oxygen in benzene solution to give in differing ratios two stereoisomeric allylic hydroperoxides, a result not in accord with an all suprafacial mechanism for the "ene" reaction.

Sir: For the "ene" reaction of alkenes with singlet oxygen there must be available an allylic hydrogen aligned roughly parallel to the plane formed by the π bond.[1] In this light the alkenes **1** and **2**[2] possess instructive structural features for elucidation of stereochemical aspects of singlet oxygen reactions. In all-chair conformations **1** and **2** belong, respectively, to C_{2v} and C_{2h} point groups and as such should be conformationally fixed models for the two all-chair conformations that cyclohexylidenecyclohexane may adopt in principle.[3] Only the equatorial face of **1** is available for a concerted all suprafacial "ene" reaction, whereas the axial face is structurally related to adamantylideneadamantane, photooxygenation of which gives a 1,2-dioxetane.[4,5] The alkene faces of **2** are equivalent but with regard to any one face only that alkylidene carbon furthest from the axial allylic hydrogen can bond in a concerted all suprafacial concerted "ene" reaction (axial rather than equatorial bonding).



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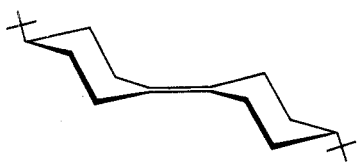

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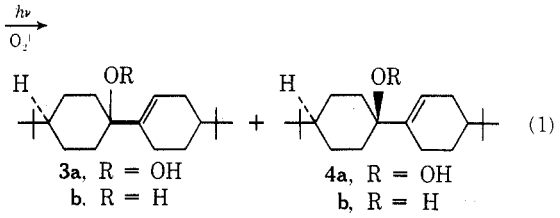
^{1}H NMR, ^{13}C NMR, and ir spectra of **1** and **2** are virtually superimposable. Substantiation of the presumed double-chair conformations for both **1** and **2** is obtained from analysis of the ^{1}H NMR spectra (100 MHz). Particularly revealing is a broadened doublet, J = 12.5 Hz, at δ 2.67 in $CDCl_3$, which is assigned to the equatorial allylic protons, which have a normal J_{gem} but small J_{vic} coupling in the chair conformation. This absorption is absent in the (temperature averaged) spectrum of cyclohexylidenecyclohexane at room temperature. Full details will be reported subsequently.

Both **1** and **2** (150 mg in 150 ml of benzene, *meso*-tetraphenylporphine sensitizer, $K_2Cr_2O_7$ filter) react smoothly with singlet oxygen. The rate of consumption is as great as that of cyclohexylidenecyclohexane itself.[6a] Within the limits of sensitivity of the detection techniques,[6b] quantitative conversion to two products assigned structures **3a** and **4a** occurred (eq 1). From **1** the ratio of **3a**:**4a** was 60:40; from **2** this ratio was 33:67. Although ir, ^{1}H NMR, and mass spectra were in accord with expectation for **3a** and **4a**, neither compound has been purified sufficiently to give a sharp melting point. The structures were verified through subsequent conversions (see below). The hydroperoxides did not



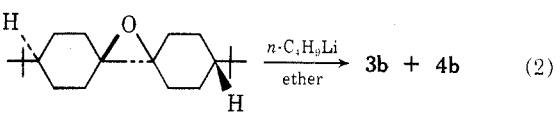
3a, R = OH
b, R = H

4a, R = OH
b, R = H

(1)

interconvert or undergo other rearrangements on standing at ambient temperature in solution for at least 1 day. Attempts to use gas chromatography caused decomposition to both 4-*tert*-butylcyclohexanone and a mixture of epoxides.[6a,7]

Reduction of crude photooxygenation mixtures with $NaBH_4$ in methanol gave quantitatively in ratios identical with the original peroxide composition the alcohols **3b** and **4b.** In our hands especially **4b** was difficult to work with owing to its ready dehydration.[8] The alcohols were ultimately separated by thin layer chromatography and purified by careful recrystallization, **3b,** mp 154–155.5°, and **4b,** mp 180.5–183°.[9] Stereochemistry is assigned to **3b** and **4b** (and by analogy to **3a** and **4a** on the basis that reduction does not affect configuration) from the much faster elution of the latter on aluminum oxide.[10] Independent structural confirmation for these structures was obtained through conversion of **2** to epoxide **5** with *meta*-chloroperbenzoic acid, followed by ring opening of **5** with strong base producing a mixture of **3b** and **4b** (eq 2). The ring opening pro-



(2)

5

ceeded only sluggishly with butyllithium and exhibited no pronounced stereoselectivity.[11]

There is no obvious reason to suppose a breakdown of the normal stereoelectronic requirement for an axially oriented allylic hydrogen in the "ene" reaction of **1** and **2.** Both olefins are fixed in double-chair conformations and the low activation energies for reaction with singlet oxygen (1.3 kcal/mol for cyclohexylidenecyclohexane in methanol)[12] indicate that the rate-determining reaction should occur through these conformations (specifically the Curtin–Hammett principle is not violated).[13,14] Subject to these restrictions, the obtainment of **4a** from **1** and **3a** from **2** is inconsistent with complete suprafacial participation of the alkenes reacting from all-chair conformations. Other explanations are demanded. Possibilities include a previously undetected antarafacial component to the "ene" reaction or the initial irreversible formation of an intermediate, perhaps a peroxirane,[5] which lives sufficiently long to be able to react, if necessary, from an attainable but energetically unfavorable flexible form in which a quasi axial hydrogen is presented.

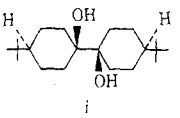
We are currently engaged in experiments to test these and other ideas.

References and Notes

(1) (a) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, **83,** 1498 (1961). (b) For an excellent review of singlet oxygen reactions, see R. W. Denny and A. Nickon, *Org. React.*, **20,** 133 (1973).
(2) R. M. Kellogg, M. Noteboom, and J. K. Kaiser, *J. Org. Chem.*, preceding paper in this issue.
(3) Cyclohexylidenecyclohexane is known to have C_{2h} geometry in the crystal: K. Sasvari and M. Löw, *Acta Cryst.*, **19,** 840 (1965).
(4) (a) J. H. Wieringa, J. Strating, H. Wynberg, and W. Adam, *Tetrahedron Lett.*, 169 (1972). (b) Both a 1,2-dioxetane and an epoxide are obtained from 7′,7′-binorbornylidene: P. D. Bartlett and M. S. Ho, *J. Am. Chem. Soc.*, **96,** 627 (1974). (c) Related observations have been made with bisbicyclo[3.3.1]-9-nonylidene: H. K. Keul, Dissertation, Karlsruhe, 1973.
(5) The factors affecting the competition between different modes of reac-

tion for singlet oxygen are the subject of much current interest: (a) N. M. Hasty and D. R. Kearns, *J. Am. Chem. Soc.*, **95**, 3380 (1973); (b) A. P. Schaap and G. R. Faler, *ibid.*, **95**, 3381 (1973); (c) P. A. Burns and C. S. Foote, *ibid.*, **96**, 4339 (1974); (d) L. N. Stephenson, D. E. McClure, and P. K. Sysak, *ibid.*, **95**, 7888 (1973).

(6) (a) Investigation of photooxygenation: G. O. Schenck and K. H. Schulte-Elte, *Justus Liebigs Ann. Chem.*, **618**, 185 (1958). (b) In benzene *t*-Bu absorptions of starting material and products are well separated and can be monitored accurately using wide sweep widths. Although they cannot be detected by the ^{1}H NMR method under these conditions other products are certainly present. Crude photooxygenation mixtures in boiling dioxane with 9,10-dibromoanthracene chemiluminesce well. When photooxygenated in methylene chloride using Methylene Blue as sensitizer, **1** after reduction gave 5–10% glycol i, likely arising from reduc-



i

tion of a 1,2-dioxetane. In a reinvestigation of the photooxygenation of cyclohexylidenecyclohexane, after reduction with $NaBH_4$ there was found in addition to the previously reported 1-(1-cyclohexenyl)-1-cyclohexanol the glycol and the epoxide of cyclohexylidenecyclohexane in the ratio 98:1:1 (by GPC).

(7) See also (a) W. F. Brill, *J. Am. Chem. Soc.*, **87**, 3286 (1965); (b) G. O. Schenck, O. A. Neumüller, and W. Eisfeld, *Justus Liebigs Ann. Chem.*, **618**, 202 (1958).

(8) Dienes are formed. Note that loss of water from **3a** and **4a** leads to two isomeric dienes.

(9) Spectral data were in accord with the proposed structures, in particular a single vinylic proton was observed in the ^{1}H NMR spectra. Satisfactory analytical data have been obtained for all new compounds except **3a** and **4a**.

(10) (a) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953); (b) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); (c) S. Winstein and N. S. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955); (d) E. W. Garbisch, Jr., and D. B. Patterson, *ibid.*, **85**, 3228 (1963).

(11) Compare with R. P. Thummel and B. Rickborn, *J. Am. Chem. Soc.*, **92**, 2064 (1970).

(12) E. Koch, *Tetrahedron*, **24**, 6295 (1968).

(13) For extensive applications of this argument, see K. Gollnick, *Adv. Photochem.*, **6**, 1 (1968).

(14) D. Y. Curtin, *Record. Chem. Progr.*, **15**, 111 (1954).

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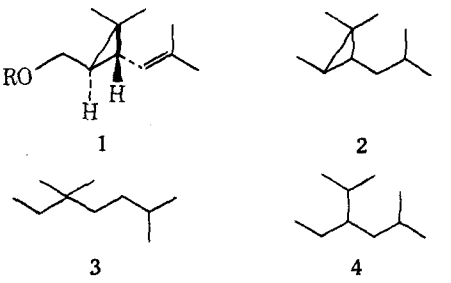
Studies on the Biogenesis of Non-Head-to-Tail Monoterpenes. The Isolation of (1*R*,3*R*)-Chrysanthemol from *Artemesia ludoviciana*[1]

Summary: The isolation of optically pure (1*R*,3*R*)-chrysanthemol from the leaves of *Artemesia ludoviciana* supports the hypothetical involvement of the corresponding pyrophosphate as a cruical intermediate in the biosynthesis of non-head-to-tail monoterpenes.

Sir: As part of a continuing study of the biosynthesis of the biologically important triterpene, squalene, we have been investigating the simpler but presumably analogous non-head-to-tail monoterpenes. Although there has been little experimental verification of any biosynthetic pathway, the available data[2] coupled with biogenetic analogies to presqualene alcohol and the known chemical[3] interconversions of the chrysanthemyl carbon skeleton with other non-head-to-tail monoterpene carbon skeletons have led to a unified hypothesis for the biosynthesis of these compounds.[4] This hypothesis requires (1*R*,3*R*)-chrysanthemyl pyrophosphate (**1**, R = pyrophosphate) as a key intermediate in the formation of the chrysanthemyl (**2**), artemesyl (**3**), and santolinyl (**4**) types of irregular monoterpenes. With the ubiquitous occurrence of phosphatases in plants, it might be expected that any plants producing **1** (R = pyrophosphate) would also have the corresponding alcohol, (1*R*,3*R*)-chrysanthemol (**1**, R = H), present.



1 **2** **3** **4**

In support of the proposed biosynthetic scheme, we wish to report the isolation of **1** (R = H) from the leaves of the sage brush, *Artemesia ludoviciana*, and further in accord with the hypothesis the natural chrysanthemol is optically pure possessing the 1*R*,3*R* absolute configuration.

The essential oils from 4 kg of fresh leaves of *A. ludoviciana* collected near Salt Lake City[5] were obtained by extraction of the plant material with pentane. Removal of the solvent and vacuum, bulb-to-bulb distillation of the remaining volatiles gave 12.5 ml of a mixture containing approximately 2% chrysanthemol as evidenced by VPC comparison to known **1** (R = H) on a 500-ft capillary column. The mixture was subjected to a vacuum distillation on a 60-cm annular spinning band column and the fractions enriched in **1** (R = H) were combined and further separated by a succession of high-pressure liquid chromatographies on a 170–200 mesh Florisil column using 1:10 ethyl acetate–hexane as the eluting solvent system. VPC analysis indicated an increase from 70 to 90 to 98% purity in the successive runs. The final purification was accomplished by preparative VPC on a 20 ft × ⅜ in. Carbowax 20M column to give 25 mg of 100% pure chrysanthemol. Spectral comparisons (NMR and ir) with authentic material as well as VPC coinjections confirmed the structure. Synthetic **1** (R = H) prepared by reduction of 97% (1*R*,3*R*)-chrysanthemic acid via its methyl ester[6] possessed an $[\alpha]_D$ of +46.9° (*c* 1.7, methylcyclohexane) while the isolated material had $[\alpha]_D$ +49.7° (*c* = 1.1, methylcyclohexane), indicating that the natural chrysanthemol is essentially 100% 1*R*,3*R*.

Evidence that the isolated **1** (R = H) could have been derived in vivo from the corresponding pyrophosphate was provided by allied studies in which we have clearly demonstrated enzymatic including phosphatase activity in leaf preparations of *A. ludoviciana*. In particular we have observed the facile conversion of known **1** (R = pyrophosphate) to **1** (R = H) in vitro by these leaf preparations.

References and Notes

(1) This work was supported by a grant from the National Institutes of Health (R01 GM20196).

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(3) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 1453 (1967); T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *J. Org. Chem.*, **36**, 1968 (1971); C. D. Poulter, S. G. Moesinger, and W. W. Epstein, *Tetrahedron Lett.*, 67 (1972); L. Crombie, P. A. Firth, R. P. Noughton, D. A. Whiting, and D. K. Woods, *J. Chem. Soc., Perkin Trans. 1*, 642 (1972); T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, *Chem. Lett.*, 503 (1972).

(4) W. W. Epstein and C. D. Poulter, *Phytochemistry*, **12**, 737 (1973); R. B. Bates and S. K. Paknikar, *Tetrahedron Lett.*, 1453 (1965).

(5) Voucher Specimen 84025 of the University of Utah Herbarium contains a pressed sample of the *Artemesia ludoviciana* used in this study.

(6) We wish to thank Professor C. D. Poulter of this department for the sample used in our comparisons.

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