(13) J. K. Yandell, D. P. Fay, and N. Sutin, *J. Am. Chem. Soc.*, **95**, 1131 (1973).
(14) C. Creutz and N. Sutin, *Proc. Natl. Acad. Sci. U.S.A.*, **70**, 1701 (1973).
(15) J. V. McArdle, H. B. Gray, C. Creutz, and N. Sutin, *J. Am. Chem. Soc.*, **96**, 5737 (1974).
(16) R. X. Ewall and L. E. Bennett, *J. Am. Chem. Soc.*, **96**, 940 (1974).
(17) T. J. Przystas and N. Sutin, *Inorg. Chem.*, **14**, 2103 (1975).
(18) B. Brunschwig and N. Sutin, *Inorg. Chem.*, **15**, 631 (1976).
(19) J. F. Endicott and H. Taube, *J. Am. Chem. Soc.*, **84**, 4984 (1962); *Inorg. Chem.*, **4**, 437 (1965).
(20) E. J. Land and A. J. Swallow, *Arch. Biochem. Biophys.*, **145**, 365 (1971).
(21) T. Flatmark, *Acta Chem. Scand.*, **19**, 2059 (1965).
(22) F. R. Salemme, J. Kraut, and M. D. Kamen, *J. Biol. Chem.*, **248**, 7901 (1973).
(23) One of the referees did point out that although the mixed-spin species is believed to exist in 0.1 M chloride at pH 2, our cyt c^3, which we suggest to be the mixed-spin species, is not identifiable from our kinetic data under these conditions. We do acknowledge this point, but also add that this does not affect our interpretation of the data, and, more important, it does not alter the reactivity order we have suggested. Our identification of cyt c^3 with the mixed-spin species is based on the fact that our independently measured rate constants in 1.0 M NaCl (pH 1.0) and in 0.1 M ClO_4^- (pH 1) are the same. Under these conditions, the mixed-spin forms are strongly believed[9,17] to be the dominant cytochrome *c* species in solution, and we suggest these to be cyt c^3. Our data in 0.1 M chloride (pH 2.0) suggest that, even if the mixed-spin species is present, its reactivity is considerably masked by that of the less protonated but far more reactive cyt c^1 (whose existence has always been inferred from rate measurement only!!). This issue confirms the fundamental difficulty of interpretation that can be associated with the complexity of the acid dependence data at low acid in this type of rate study.

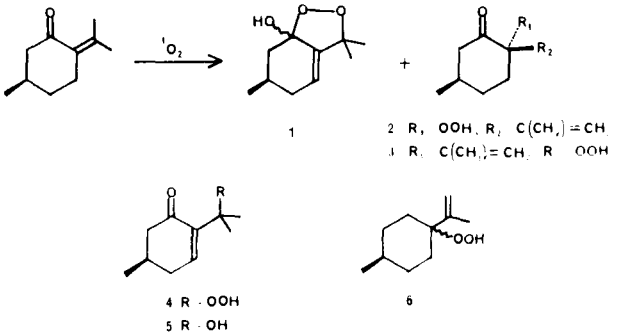
Communications to the Editor

Reaction of Singlet Oxygen with α,β-Unsaturated Ketones and Lactones

Sir:

The reaction of singlet oxygen ($^1O_2$) with alkenes has been extensively studied because of its synthetic utility,[1] its implications in environmental and biological processes,[2] and the mechanistic interest associated with this reaction.[3-6] Despite this intense investigation, there are relatively few examples of the successful oxidation of alkenes that are substituted with electron-withdrawing groups.[7] Numerous examples of the attempted photooxygenation of 3-keto-Δ^4 steroids have shown that these types of enones are unreactive toward singlet oxygen,[1a] a fact which is not surprising since singlet oxygen has been shown to be weakly electrophilic.[8] However, in our previous studies on the conversion of (*R*)-(+)-pulegone into its enantiomer, singlet oxygen proved to be the reagent of choice for the initial allylic oxidation of this enone.[9] We now report that the reactivity of α,β-unsaturated ketones and lactones toward singlet oxygen is strongly dependent on the conformation of the unsaturated system. Those α,β-unsaturated carbonyl systems which prefer (or are constrained to) the s-cis conformation are rapidly oxidized by singlet oxygen, whereas those systems which prefer the s-trans conformation react slowly or not at all.

The photooxygenation of (*R*)-(+)-pulegone using a variety of sensitizers (rose bengal, zinc tetraphenylporphin, methylene blue, and Photox[10]) and in a variety of solvents (benzene, methylene chloride, and methanol) affords, after evaporation of solvent and flash chromatography,[11] **1**,[12] **2**, and **3**[13] in 75, 6, and 6% yields, respectively.[14] Compound **1**, which is the hemiperketal of the hydroperoxyenone **4**, is quantitatively reduced to **5**[15] on exposure to excess triphenylphosphine, triethyl phosphite, or aqueous stannous chloride.



The regioselectivity of the reaction of **1** with singlet oxygen is surprising since the photooxygenation of the corresponding alkene, isopropylidene-4-methylcyclohexane, occurs exclusively with migration of the double bond away from the ring, to give **6**,[16] and also since singlet oxygen reactions do not normally show a strong Markownikoff effect.[4c,17] To explore the reasons behind this change in regioselectivity, the reaction of singlet oxygen with a series of α,β-unsaturated carbonyl systems was studied. The results are summarized in Table I.

That the products shown in Table I arise from reaction with singlet oxygen and not from radical processes is indicated by the complete inhibition of photooxygenation in the presence of 10 mol % 1,4-diazabicyclo[2.2.2]octane[18] and the lack of inhibition of photooxygenation in the presence of 10 mol % 2,6-di-*tert*-butylcresol, a free-radical inhibitor. Also, in the cases of entries 1 and 6 of Table I the same products are obtained in 58 and 69% yields, respectively, when the enone (5 mmol) is added to a solution of triphenyl phosphite ozonide (25 mmol) in methylene chloride at −78 °C and the solution is allowed to warm to room temperature.[19]

Any mechanistic explanation of the data presented in Table I must account for both the large differences in the β values for s-cis and s-trans α,β-unsaturated carbonyl systems and the preference for the formation of the α,β-unsaturated oxidation product. Both the "approach control" mechanism of Fukui[4b] and the zwitterionic peroxide mechanism of Jefford[3c] lead to incorrect predictions of the major product in the above reactions. The biradical mechanism proposed by Goddard[5] correctly predicts the major product, but does not explain the observed differences in reactivity.

Paquette and Liotta[20] have proposed that the site selectivity observed in the reaction of singlet oxygen with certain polyenes can be predicted from the ionization potentials of the various olefinic systems. Their proposal suggests that differences in reactivity between s-cis and s-trans conformers may be a reflection of conformational effects[21] on the ionization potentials of the α,β-unsaturated carbonyl system. Therefore, we have measured the n and π ionization potential for several of the compounds in Table I. These data are shown in Table II.

Even though the conformation of the π system does have a small effect on the ionization potential as shown by the first two entries of Table II, there is no correlation between ionization potential and reactivity toward singlet oxygen, showing that electronic effects are not the controlling factor in these systems.

The mechanism which we propose to explain the reactivity differences between s-cis and s-trans α,β-unsaturated carbonyl

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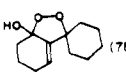
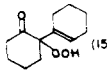
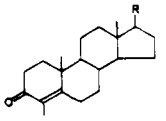
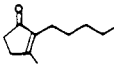
Table I. Reaction of Singlet Oxygen with α,β-Unsaturated Carbonyl Systems[a]

ENTRY	REACTANT	β-VALUE[b]	PRODUCT (YIELD)[c]
1		0.12	1 (75) ; 2 (6) ; 3 (6)
2		0.34	 (78) ;  (15)
3		>200	N.R.[d]
4	 R : OH R : C_7H_{11}	>200	N.R.[d]
5		0.65	 (81)
6		0.06	 (88)
7		0.25	 (84)
8		>200	N.R.[d]
9		28	 (24)

[a] All photooxydations were carried out using 1–2 M solutions of substrate in CH_2Cl_2 or methanol at 0 °C. In CH_2Cl_2 Photox was used as the sensitizer. In methanol rose bengal was the sensitizer. Entries 1 and 4 were also photooxidized in CH_2Cl_2 and benzene using methylene blue as the sensitizer. The observed regioselectivity was independent of solvent and sensitizer. [b] β values were determined using linalool ($\beta = 0.18$) as the standard.[1a] [c] Yields are reported for chromatographically purified materials. [d] Substrate was recovered unchanged after prolonged photooxygenation.

Table II. Ionization Potentials of α,β-Unsaturated Ketones and Lactones

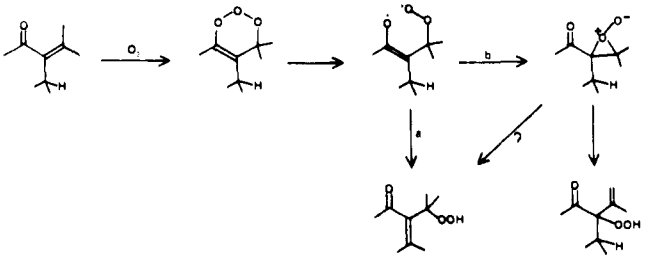
compd	πIP,[a] eV	ηIP,[a] eV
(*R*)-(+)-pulegone	8.90[b]	8.90[b]
2-ethyl-3-methylcyclohex-2-enone	9.07[b]	9.07[b]
2-cyclopentylidenecyclopentanone	8.80	8.90
3,4-dihydrojasmone	9.00[b]	9.00[b]
α-isopropylidene-γ-butyrolactone	9.48	9.89
3,4-dimethylpent-3-en-2-one	9.20[b]	9.20[b]

[a] All ionization potentials are vertical, ±0.05 eV, or, if broad, they refer to band maxima. [b] The η and π bands overlap in the PES spectrum.

systems toward singlet oxygen is shown in Scheme I.

The initial [4 + 2] cycloaddition of singlet oxygen and the enone to give the 1,2,3-trioxine is analogous to the well-known addition of singlet oxygen to s-cis dienes.[17a,22] Thermolytic cleavage of the weak oxygen-oxygen bond to give a stabilized biradical followed by abstraction of the β-hydrogen atom (via a cyclic, six-membered transition state, path a) gives rise to the major product in the above reactions. The minor products which are observed in entries 1 and 2 of Table I could arise from the energetically less favorable collapse of the diradical

Scheme I



to the perepoxy ketone (path b), followed by proton abstraction from the γ position.[23]

Currently, studies are underway to detect and intercept the proposed 1,2,3-trioxine intermediate.

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References and Notes

(1) (a) R. W. Denny and A. Nickon, *Org. React.*, **20**, 133 (1973); (b) G. Ohloff, *Pure Appl. Chem.*, **43**, 481 (1975).
(2) C. S. Foote in "Free Radicals in Biology", W. A. Pryor, Ed., Academic Press, New York, 1976.
(3) For examples of proposed zwitterionic intermediates, see (a) C. W. Jefford and C. G. Rimbalt, *Tetrahedron Lett.*, 2375 (1977); (b) I. Saito, M. Imuta, Y. Takahashi, S. Matsugo, and T. Matsuura, *J. Am. Chem. Soc.*, **99**, 2005 (1977); (c) C. W. Jefford, *Tetrahedron Lett.*, 985 (1979); (d) C. W. Jefford and C. G. Rimbault, *J. Am. Chem. Soc.*, **100**, 6437 (1978).
(4) For examples of proposed perepoxide intermediates, see (a) G. Rousseau, P. LePerchec, and J. M. Conia, *Tetrahedron Lett.*, 2517 (1977); (b) S. Inagaki, H. Fujimoto, and K. Fukui, *Chem. Lett.*, 749 (1976); (c) K. Kopecky and H. J. Reich, *Can. J. Chem.*, **43**, 2265 (1965); (d) W. Fenical, P. R. Kearns, and P. Radlik, *J. Am. Chem. Soc.*, **91**, 7771 (1969); (e) L. M. Stevenson, D. E. McClure, and P. K. Sysak, *ibid.*, **95**, 7888 (1973).
(5) For examples of proposed biradical intermediates, see (a) L. B. Harding and W.A. Goddard, *J. Am. Chem. Soc.*, **99**, 4520 (1977); (b) L. G. Harding and W. A. Goddard, *Tetrahedron Lett.*, 747 (1978).
(6) For examples of proposed concerted ene mechanisms, see (a) A. Nickon and W. L. Mendelson, *Can. J. Chem.*, **43**, 1419 (1965); (b) C. S. Foote, *Pure Appl. Chem.*, **27**, 635 (1971); (c) A. Nickon, J. B. DiGiorgio, and P. J. L. Daniels, *J. Org. Chem.*, **38**, 533 (1973).
(7) K. H. Schulte-Elte, *Jahresver. Deutsch. Hochschulschr.*, **78**, 348 (1962); W. Eisfeld, Ph.D. Dissertation, University of Göttingen, 1958.
(8) A. Nickon and W. L. Mendelson, *J. Am. Chem. Soc.*, **87**, 3921 (1965).
(9) H. E. Ensley and R. V. C. Carr, *Tetrahedron Lett.*, 513 (1977); see also W. Skorianetz, H. Giger, and G. Ohloff, *Helv. Chim. Acta*, **54**, 1797 (1971).
(10) Photox is a polymer-bound form of rose bengal; see E. C. Blossey, D. C. Neckers, A. L. Thayer, and A. P. Schaap, *J. Am. Chem. Soc.*, **95**, 5820 (1973).
(11) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(12) (a) All new compounds reported herein gave satisfactory, ^{13}C, ^1H, IR, and MS data. All new compounds (except the peroxides) gave satisfactory analytical data. (b) The hemiperketal 1 is easily distinguished from the expected hydroperoxy ketone **4** by ^{13}C NMR (150.1, 119.5, 102.4, 82.3, 38.8, 33.8, 28.4, 25.7, 25.5, and 21.3 ppm), ^1H NMR [δ 5.72 (vinyl)], and IR spectra. That the cyclization is spontaneous, and not caused by the chromatographic conditions, has been demonstrated by spectroscopic examination (IR, ^{13}C, ^1H) of the crude reaction mixture after photooxygenation (or reaction with triphenyl phosphite ozonide) and removal of the solvent under vacuum.
(13) The isomeric α-hydroperoxyenones **2** and **3** were not separated but showed the expected 20-line ^{13}C spectrum (213.0, 210.9, 140.3, 139.2, 120.0, 117.6, 92.0, 19.1, 49.5, 47.7, 35.0, 32.7, 31.6, 30.7, 30.0, 28.4, 21.9, 19.9, 19.0, and 18.5 ppm) and a 1:1 ratio of **2:3**.
(14) All yields refer to isolated yields of chromatographically and spectrally pure compounds.
(15) Spectral data for **5**: ^{13}C NMR 202.0, 143.6 (two carbons), 71.7, 47.4, 34.1, 30.1, 29.0, 28.9, and 20.9 ppm; ^1H NMR δ 7.26 (vinyl); IR 1665 cm^{-1} (C=O).
(16) E. Klein and W. Rojahn, *Tetrahedron*, **21**, 2173 (1965).
(17) (a) C. S. Foote, *Acc. Chem. Res.*, **1**, 104 (1968); (b) C. S. Foote, Y. C. Chang, and R. W. Denny, *J. Am. Chem. Soc.*, **92**, 5216, 5218 (1970); (c) C. S. Foote and R. W. Denny, *ibid.*, **93**, 5162, 5168 (1971).
(18) C. Ouannes and T. Wilson, *J. Am. Chem. Soc.*, **90**, 6527 (1968).
(19) R. W. Murray and M. L. Kaplan, *J. Am. Chem. Soc.*, **91**, 5358 (1969).
(20) L. A. Paquette and D. C. Liotta, *Tetrahedron Lett.*, 2681 (1976).
(21) R. S. Brown and R. W. Marcinko, *J. Am. Chem. Soc.*, **100**, 5721 (1978).
(22) G. O. Schenk, *Angew. Chem.*, **69**, 579 (1957).
(23) An alternative explanation which involves preferential quenching of singlet oxygen by s-trans α,β-unsaturated ketones appears unlikely since the

addition of dihydrojasmone (final concentration of 0.6 M) to a solution of (+)-pulegone (0.16 M) in methylene chloride did not affect the rate of oxygen consumption.

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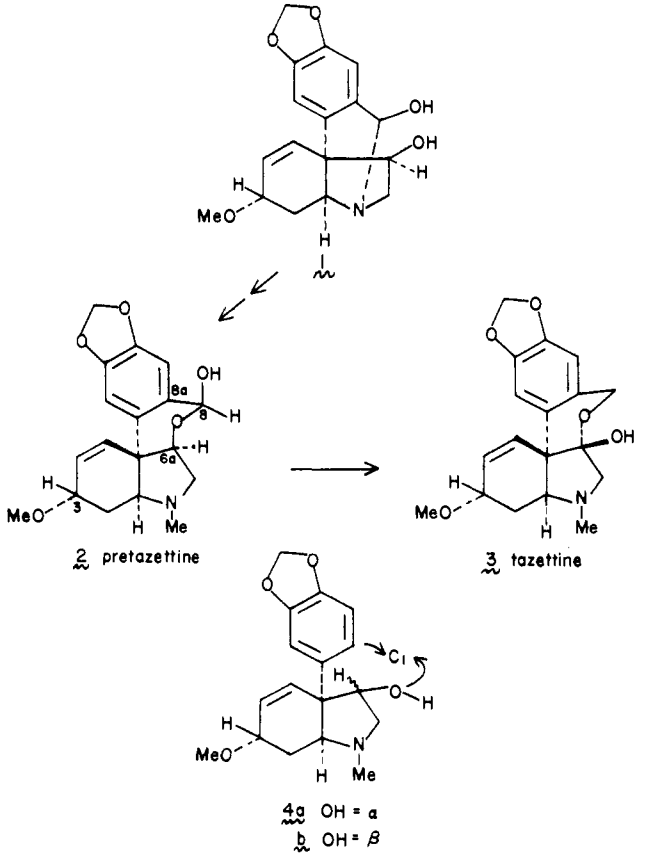
Total Synthesis of *dl*-Tazettine

Sir:

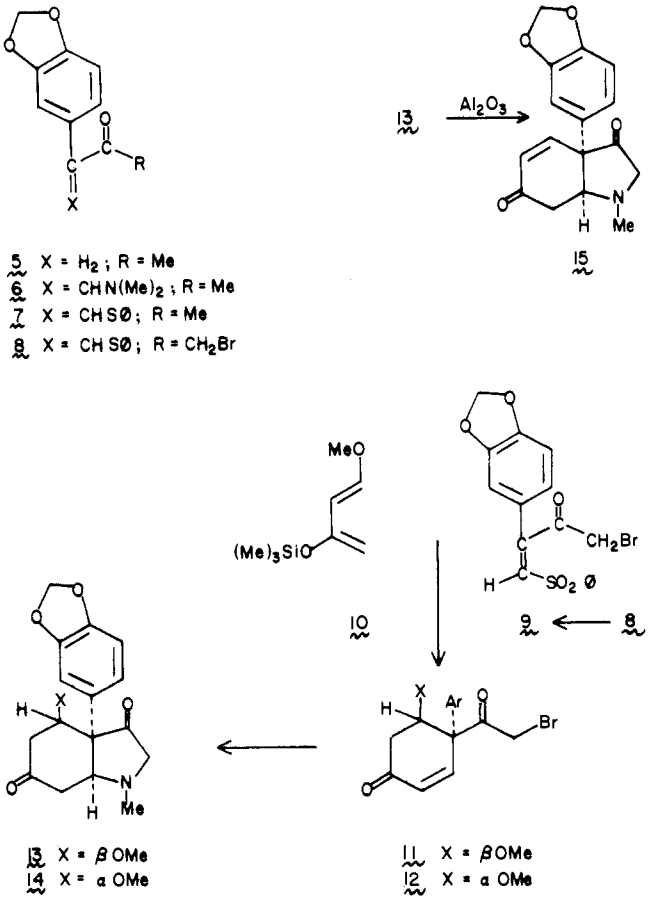
The structural relationship of the amaryllidaceae alkaloids haemanthidine (**1**) methiodide, pretazettine (**2**), and tazettine (**3**) was unveiled by Wildman and co-workers.[1,2] Shortly thereafter, Hendrickson and Fisch described a stereospecific and ingenious total synthesis of haemanthidine.[3] Given the connectivity between these alkaloids[1,2] Hendrickson's synthesis of **1** also constituted, in a formal sense, the total syntheses of **2** and **3.** Subsequent to Hendrickson's achievement, another total synthesis of *dl*-**1** was reported by Tsuda et al.[4,5] Following Wildman's protocols, racemic **1** was converted into racemic **2.**[5]

Interest in this family of alkaloids has been heightened as a consequence of the antitumor properties which have been ascribed to pretazettine by Furusawa.[6] We have thus been attempting to achieve the total syntheses of **2** and **3** by a direct strategy rather than by routes fundamentally directed toward haemanthidine. Our approach projected the synthesis of a precursor such as **4,** under the presumption that a suitable C_1 fragment (i.e., C_8)[1] could be inserted at a terminal stage between an oxygen at C_{6a} and carbon C_{8a} of the aromatic ring. It was hoped that a hydroxyl group would provide the required guidance for this operation.

Below is provided an interim progress report on this investigation. Concise (11 steps) stereoselective constructions of both C_{6a} epimers of **4** have been realized. For the moment, we have been unable to achieve the required introduction of the C_1 unit from epimer **4b.** However, this interpolation has been accomplished via epimer **4a,** thus leading to the total syntheses of 6a-epipretazettine (**21**) and tazettine (**3**).



Our first synthetic subgoal was the enedione **15.** This compound, mp 158-159 °C, was reached in eight steps starting with the known[7] and readily available 2,3-methylenedioxyphenylacetone (**5**). Treatment of **5** with *N,N*-dimethylformamide dimethyl acetal (80 °C, 3.5 h, room temperature) afforded a quantitative yield of **6,** mp 87-88 °C,[8] which was converted in 90% yield into *E,Z* ketosulfides **7**[8] by exchange with thiophenol.[9] These were transformed into the bromomethyl sulfides **8**[8] via enol silylation [(i) LDA, THF, −78 °C; (ii) Me_3SiCl, −78 °C → room temperature] followed by bromination (*N*-bromosuccinimide). Oxidation of **8** (2 equiv of *m*-chloroperoxybenzoic acid, methylene chloride, 0 °C → room temperature) afforded the corresponding sulfones **9**[8] as a 5:1 mixture of stereoisomers in 55% yield from **7.** These sulfones were separated by chromatography on silica gel and elution with 5% ethyl acetate-benzene. The major (more polar) isomer, served as a dienophile[10a,b] toward diene **10.**[10c,d,11,12] Diels-Alder reaction was carried out at 70 °C in benzene in a sealed tube for 3 h. Chromatography on silica gel afforded a 54% yield of the 4,4-disubstituted cyclohexenones **11**[8] and **12**[8] which, after reaction with methylamine (40% aqueous solution in THF, room temperature, 30 min) afforded an 80% yield of a 9:1 mixture of **13**[8]-**14**[8]. Adsorption of **13** on neutral alumina[13] for 30 min followed by elution afforded a 45% yield of **15**[8] as well as 42% recovered **13** which are recycled in the same way.



The required chiralities at carbons 3 and 6a were established as follows. The enone could be selectively reduced with diisobutylaluminum hydride in tetrahydrofuran. There was thus obtained a 3:1 ratio of alcohols **16**[8] and **17.**[8] The β-alcohol, **16,**

0002-7863/80/1502-2838$01.00/0