

ENAMINE-SINGLET OXYGEN REACTIONS.

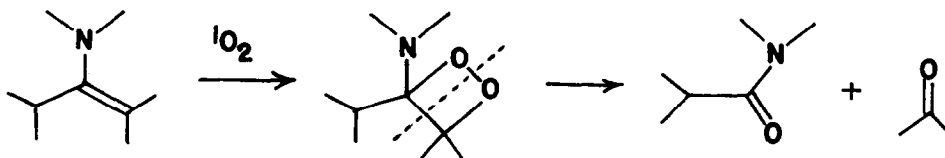
α -DIKETONES FROM INTERMEDIATE AMINO DIOXETANES

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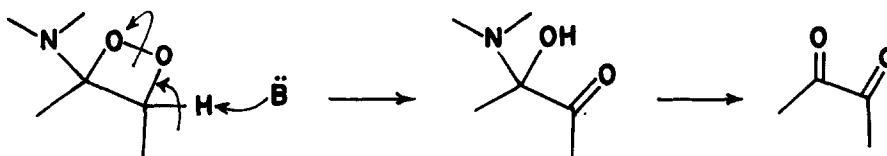
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Among the types of reactions in which singlet oxygen takes part, the 1,2-addition to enamines is of special interest in view of the widespread involvement of the enamine grouping in biological systems. Thus far, studies on the photooxygenation of enamines have been limited to acyclic systems, and have shown that the double bond undergoes cleavage to carbonyl fragments.^{1,2}

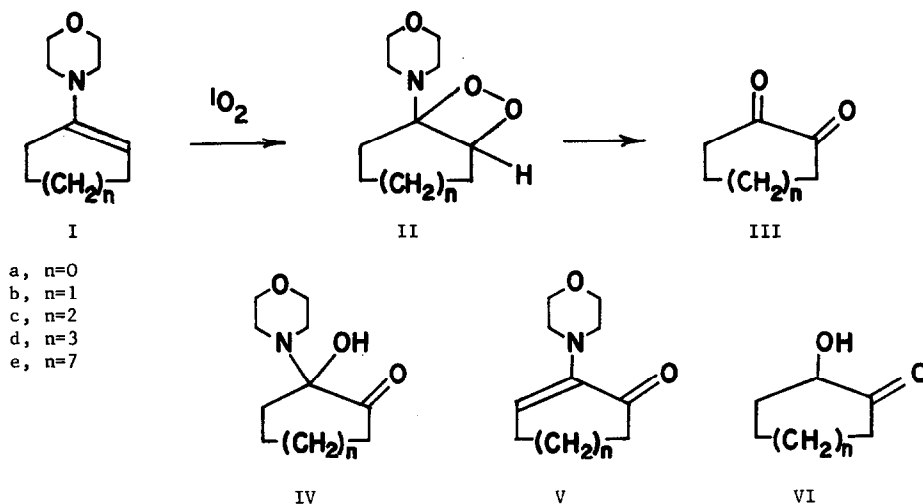


We now report that in the photooxygenations of the enamines of a series of cyclic ketones the major reaction products are α -diketones or their enamine derivatives.^{2a} As in the open chain cases, dioxetanes are intermediates in these oxidations.^{3,4,5} The present work shows that these dioxetanes may undergo cleavage of the O-O bond by a β -elimination mechanism.⁶

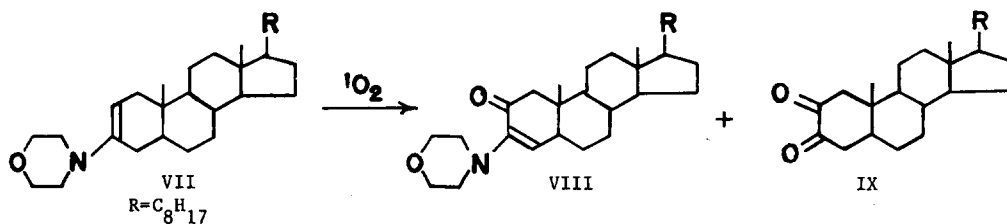


In Scheme I are listed the enamines (I) investigated in the present work and the products (II, III, IV and V) obtained in the photooxygenation. As is outlined below, the reactions generally led directly to α -diketones (III) when conducted at room temperature in methanol. At low temperatures (-78°) dioxetanes (IIb, IIc, IId) could be isolated, and these were shown to be intermediates in the formation of products corresponding to III, IV and V. Details of the procedures are given below.

A solution of *N*-cyclohexenylmorpholine (Ib) (5 mmol) in methanol was photooxygenated at room temperature using methylene blue as sensitizer and a Sylvania "Sun Gun" (625 w) light source. One equivalent of oxygen was absorbed within 30 min,⁷ the reaction mixture treated with phenylhydrazine in glacial acetic acid (10 mmol), and then allowed to stand overnight. Washing the solution with bicarbonate, drying, evaporation of solvent and chromatography on silica gel (methylene chloride elution) yielded the bis-phenylhydrazone of cyclohexane-1,2-dione, mp 152° (75%).



In the analogous photooxidations of Ia, Ic, and Id the corresponding α -diketones were isolated as bis-phenylhydrazones or bis-DNP's (30-50%), while a somewhat lower yield of product (12%) was observed in the case of Ie. Photooxidation of 3-morpholino-cholest-2-ene (VII)⁸ in absolute ether at -78° yielded (50%) (ratio ca 1:1) cholestan-2,3-dione (IX) mp 139-140° and 3-morpholino-cholest-3-ene-2-one (VIII) mp 176-177°. *Anal.* Calcd. for C₃₁H₅₁NO₂ (VIII): C, 79.26; H, 10.94; N, 2.98. Found: C, 79.18; H, 11.12; N, 2.81.



When the photooxidations of Ib-d were carried out at low temperatures in dimethyl ether it was possible to isolate dioxetane intermediates. N-Cyclohexenylmorpholine Ib (10 mmol) and bis-acenaphthalenethiophene (10 mg) in methylene chloride were added to pre-cooled dimethyl ether and photooxidized at -78° until one molar equivalent of oxygen was absorbed. As the reaction proceeded, a white crystalline product separated from the solution. Washing this solid with cold dimethyl ether and removal of solvent at -78° (0.5 mm) for 20 hr yielded the crystalline dioxetane IIb (55%).⁹ *Anal.*¹⁰ Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03; mol wt 199. Found: C, 59.92; H, 8.74; N, 6.88; mol wt (freezing pt of $CHCl_3$) 249; ir peaks¹¹ at 1155, 1100, 975 and 840 cm^{-1} . The dioxetane could be stored at -78° under anhydrous conditions for several days but underwent violent decomposition if allowed to warm up to room temperature.

When IIc was dissolved in pre-cooled methanol at -60° and the solution brought to room temperature, followed by removal of solvent *in vacuo*, the keto aminal (IVc) was obtained as an unstable oil; ir, 3450 and 1715 cm^{-1} . An ethyl ether solution of this oil, passed through a short column of silica gel, yielded 1,2-cycloheptanedione, while a benzene solution of IVc warmed for one hr at reflux gave 2-morpholino-cyclohept-2-ene-1-one (Vc). Treatment of the dioxetane IIb with sodium in liquid ammonia yielded α -diketone IIb. With triphenylphosphine in methylene chloride, the α -ketol (VIb) could also be formed along with α -diketone.

Reactions of enamines of open-chain ketones under the above conditions gave mixed results. With the morpholino enamine of 1,3-diphenylpropanone, photooxygenation produced only cleavage of the double bond, forming amide and ketone. On the other hand, the reaction of singlet oxygen with the morpholino enamine of 3-pentanone at -78° in dry ether gave a significant amount of α -diketone (28%) along with the usual cleavage products.

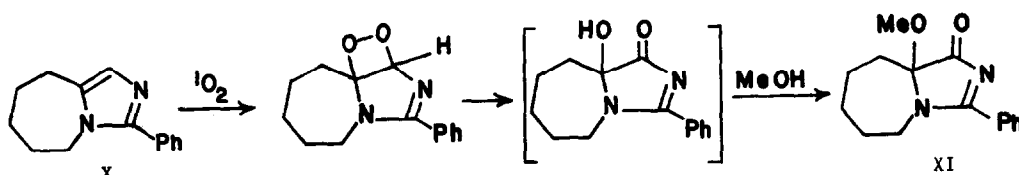
Further studies are in progress on the reactions of enamines of ketones and $\alpha,8$ -unsaturated ketones with molecular oxygen.

Acknowledgment: Support of this work by Grant GM-13854 from the National Institutes of Health is gratefully acknowledged.

Footnotes and References

1. (a) C.S. Foote and J.W.-P. Lin, *Tetrahedron Letters*, 3267 (1968). (b) J. Huber, *ibid.*, 3271 (1968). (c) C.S. Foote, A.A. Dzakpasu and J.W.-P. Lin, *Tetrahedron Letters*, in press.
2. Heterocyclic systems may undergo related cleavage with singlet oxygen to form dicarbonyl fragments: (a) T. Matsuura and I. Saito, *Tetrahedron Letters*, 3273 (1968); also, (b) H.H. Wasserman, K. Stiller and M.B. Floyd, *ibid.*, 3277 (1968).

- 2a. The autoxidation of enamines and Schiff bases of α,β -unsaturated ketones leads to unsaturated 1,4-diones. These reactions are catalyzed by metal ions and appear to take place by a free-radical chain process. S.K. Malhotra, J.J. Hostyhek, and A.F. Lundin, *J. Amer. Chem. Soc.*, 90, 6565 (1968).
3. Dioxetane intermediates in singlet oxygen-enamine reactions have previously been identified and partially characterized. See references Ia, Ic.
4. For a novel rearrangement of the dioxetane of an enamino ketone, see K. Orito, R.H. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 96, 1944 (1974).
5. For other reports of dioxetane formation in singlet oxygen reactions, see (a) P.D. Bartlett and A.P. Schaap, *J. Amer. Chem. Soc.*, 92, 3223 (1970); (b) S. Mazur and C.S. Foote, *ibid.*, 92, 3225 (1970).
6. We have found (H.H. Wasserman and M.L. Wolfe, unpublished work, from the doctoral dissertation of M.L. Wolfe, Yale University (1970)) that in the photooxygenation of the imidazole (X) an analogous cleavage of a dioxetane intermediate appears to take place, forming XI.



7. In the absence of both sensitizer and visible light no uptake of oxygen was observed.
8. C. Djerassi and B. Tursch, *J. Org. Chem.*, 27, 1041 (1962).
9. Dioxetanes IIa and IIe were not isolated. For dioxetane IIc the mol wt calcd. for $C_{11}H_{19}NO_3$ is 213. Found: mol wt 197. Elemental analysis of dioxetane IIc shows: Calcd. for $C_{11}H_{19}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.90; H, 8.87; N, 6.10.
10. Elemental analyses and molecular weight determinations on the dioxetanes were performed by R. Rittner, Olin Corp., New Haven, Conn. The freezing point depression constant (K_f) of $CHCl_3$ was measured using pure azobenzene as solute.
11. The low temperature i.r. cell was constructed according to the specifications given by J. Powling and H.F. Bernstein, *J. Amer. Chem. Soc.*, 73, 1815 (1951).