The Cleavage of Aromatic Nuclei with Singlet Oxygen: Significance in Biosynthetic Processes

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THE oxidative cleavage of aromatic nuclei is an important step in the biogenesis of many natural products.[1] In many of the known examples this transformation may be expressed by (I) to (II), where R may be a side chain, a hydroxy-group, or a hydrogen atom. This reaction requires an oxygenase enzyme and molecular oxygen.[2] In at least one case it has been demonstrated that both of the introduced oxygen atoms originate from the same molecule of oxygen,[3] *i.e.* a dioxygenase enzyme is involved and this observation has been rationalized by way of an intermediate dioxetane (III).[4]

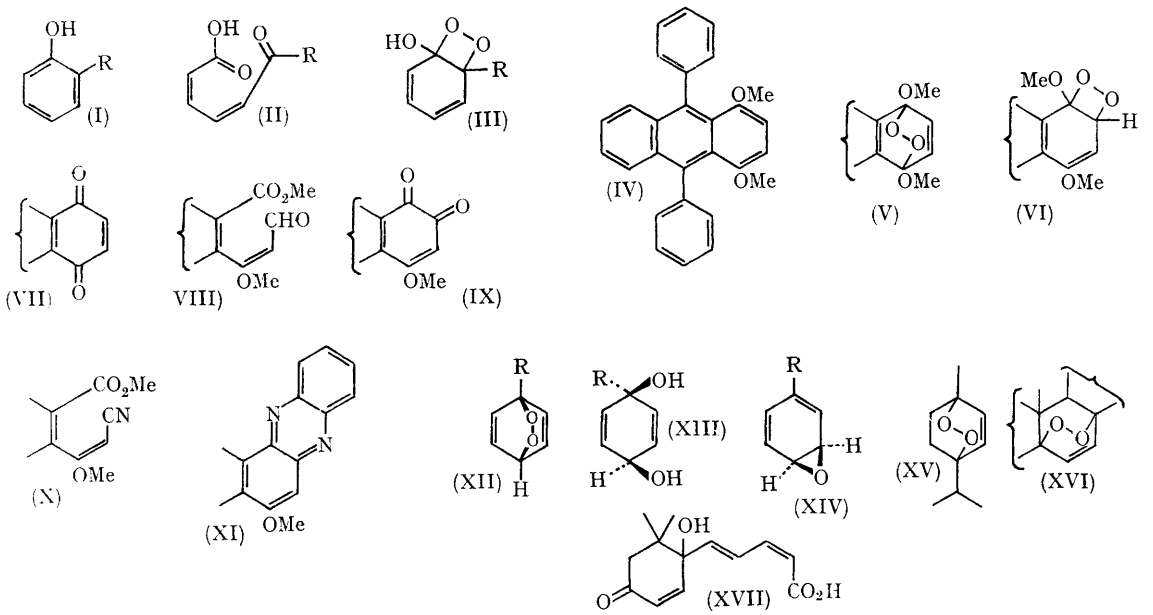
It has been our contention for some time[5] that many biological oxidations of unsaturated systems may involve the enzymic generation of a species which is equivalent in its oxidative powers to singlet oxygen. Therefore we have examined the possibility of simulating aromatic ring cleavage by use of singlet oxygen, with results which are reported here.[6] The anthracene (IV) absorbed one molecule of oxygen on photolysis with production of the endo-peroxide (V), [λ_{max} (Et_2O) 240 mμ (log ϵ 4·6), 281 mμ (log ϵ 4·12), 316 mμ (log ϵ 3·11), 331 mμ (log ϵ 3·08); n.m.r. ($CDCl_3$) τ 2·63 (m, 14 H), 3·03 (s, 2 H), 6·78 (s, 6 H)], confirming the recent reassignment of structure by Dufraisse and his co-workers.[7] We attempted to rearrange (V) to the dioxetane (VI) in aqueous acid, but only the *p*-quinone (VII) was produced. When the rearrangement was conducted in anhydrous acidic non-nucleophilic media (ethereal hydrogen chloride or hydrogen chloride in benzene) the desired cleavage was obtained, as a mixture of aldehyde ester (VIII) and the *o*-quinone (IX). The aldehyde (VIII)† [λ_{max} (EtOH) 233 mμ (log ϵ 4·65), 290 mμ (log ϵ 4·01); ν_{max} (Nujol) 1730, 1653, and 1600 cm.$^{-1}$; n.m.r.: ($CDCl_3$) τ 0·67 (d, 1 H; J 8 c./sec.), 4·60 (d, 1 H; J 8 c./sec.), 2·5 (m, 14 H), 6·5 (s, 3 H), 6·58 (s, 3 H); mass spectral M 422] was transformed *via* its oxime to the nitrile (X), [m.p. 209—211°; [λ_{max} (EtOH) 228 mμ (log ϵ 4·70), 294 mμ (log ϵ 4·04); ν_{max} ($CHCl_3$) 2220, 1730, and 1615 cm.$^{-1}$; n.m.r. ($CDCl_3$) τ 2·50 (m, 14 H), 5·50 (s, 1 H), 6·48 (s, 3 H), 6·55 (s, 3 H); mass spectral M 419], thereby confirming its functionality. The *o*-quinone (IX) [λ_{max} (EtOH) 228 mμ (log ϵ 4·61), 298 mμ (log ϵ 4·58), 420 mμ (log ϵ 3·76); ν_{max} ($CHCl_3$) 1645 and 1590 cm.$^{-1}$, n.m.r. ($CDCl_3$) τ 2·56 (m, 14 H), 3·10 (s, 1 H), 6·48 (s, 3 H); mass spectral M 390], yielded a quinoxaline (XI) when treated with *o*-phenylene diamine, as required of its formulation. These compounds were also produced by irradiation of the anthracene in the presence of acids, and also on extended irradiation in ether, since acids are produced by solvent autoxidation. This latter pathway can be blocked by base (pyridine). An analogous acid-catalyzed rearrangement of an endo-peroxide would explain the observed products in the photochemical transformations of tropolones.[8]

These experiments demonstrate that 1,4-peroxides may be transformed by acid catalysis to cleavage products of the type found in aromatic dioxygenase enzymes and therefore open up the possibility of such species being intermediates in these biological processes. They do not at present exclude the intermediacy of a 1,2-peroxide formed by an initial rearrangement of the 1,4-product.

Furthermore the same 1,4-bridged endo-peroxides, *e.g.* (XII), may be involved in the so-called NIH shift,[9] since reduction to the diol (XIII) followed by a symmetry allowed dehydration to the epoxide (XIV), provides a convenient rationalization of the 1,2-shift of substituents observed in these reactions. It is also significant that compounds containing the valence tautomeric oxepin have now been isolated from natural sources.[10]

In this general context it is to be noted that similarities between dye-sensitized oxygenations and biological processes have been pointed out several times in the literature,[11] and more recently the intermediacy of the singlet excited state of molecular oxygen has been proven for the *in vitro* systems.[12] Since the lowest singlet level, $^1\Delta g$, lies some 22 kcal. above the ground state[13] it seems likely that the high energy requirement and spin change be overcome by complexation of the oxygen molecule with an enzymically bound metal atom. There are a number of natural products which appear to be good candidates for such dioxygenase reactions, *e.g.* ascaridole (XV)[14] and steroidal ring-B peroxides (XVI).[15] The latter are particularly significant since they have been obtained from the diene and liver tissue in the dark.[16]

† Satisfactory analytical data has been obtained for all new compounds.



Abscission (XVII) has been proposed as being biosynthesized from a singlet-oxygen type of addition to a diene precursor.[17] In summary the occurrence of *cisoid*-1,3-dienes in Nature leads to expectation of oxidized metabolites derived from the respective endo-peroxides.

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[1] Many specific examples have been collected by R. Thomas, in "Biogenesis of Antibiotic Substances", published by the Czechoslovak Academy of Sciences. Prague, 1965, p. 155.

[2] The present extensive literature has been reviewed in several places: (a) O. Hayaishi, ed., "Oxygenases", Academic Press, New York, 1962; (b) D. W. Ribbons, *Ann. Report Prog. Chem.*, 1965, **62**, 445; (c) T. E. King, H. S. Mason, and M. Morrison, "Oxidases and Related Redox Systems", Wiley, New York, 1965; (d) K. Block and O. Hayaishi, "Biological and Chemical Aspects of Oxygenases", Maruzen, Tokyo, 1966.

[3] N. Itada, *Biochem. Biophys. Res. Comm.*, 1965, **20**, 149.

[4] Ref. 2(c), p. 286.

[5] These ideas were first described by J. E. Baldwin in a colloquium at Imperial College, London, November, 1965.

[6] A cleavage of the heterocyclic part of a 3-hydroxyflavanone system has been recorded by T. Matsuura, H. Matsushima, and H. Sakamoto (*J. Amer. Chem. Soc.*, 1967, **89**, 6370) who notes the possibility of this being a good model for the *in vivo* process.

[7] C. Dufraisse, J. Rigaudy, J. Basselier, and N. K. Cuong, *Compt. rend.*, 1965, **260**, 5031.

[8] E. J. Forbes and J. Griffiths, *J. Chem. Soc.* (*C*), 1967, 601.

[9] G. Guroff, J. W. Daly, D. M. Jerina, J. Renson, B. Witkop, and S. Udenfriend, *Science*, 1967, **157**, 1524.

[10] R. Nagarajan, L. L. Huckstep, D. H. Lively, D. C. DeLong, M. M. Marsh, and N. Neusse, *J. Amer. Chem. Soc.*, 1968, **90**, 2980.

[11] (a) K. Alder and M. Schumacher, *Fortschr. Chem. Org. Naturstoffe*, 1953, **10**, 8; (b) C. Dufraisse, *International Union of Pure Applied Chem.*, 1955, 27, published as Supplement to *Experientia* in June, 1955; (c) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, 1961, **83**, 1498; (d) W. Waters and E. McKeown, *J. Chem. Soc.*, (*B*), 1966, 1040; (e) W. Bergmann and M. B. Meyers, *Annalen*, 1959, **620**, 46.

[12] C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.*, 1964, **86**, 3879, 3880.

[13] G. Herzberg, "Molecular Spectra and Molecular Structure. I. Spectra of Diatomic Molecules", D. Van Nostrand New York, 1950, p. 560.

[14] A. Halpern, *J. Amer. Pharmacol. Assoc.*, 1948, **37**, 161.

[15] (a) P. Wieland and V. Prelog, *Helv. Chim. Acta*, 1947, **30**, 1028; (b) D. Dvornick, M. Kraml, J. Dubec, M. Givner, and R. Gandry, *J. Amer. Chem. Soc.*, 1963, **85**, 3309.

[16] G. A. Blondin, B. D. Kulkarni, and W. R. Nes, *J. Amer. Chem. Soc.*, 1964, **86**, 2528.

[17] J. W. Cornforth, B. V. Milborrow, and G. Ryback, *Nature*, 1965, **206**, 715.