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THE REACTIONS OF HETEROCYCLIC SYSTEMS WITH SINGLET OXYGEN. PHOTOSENSITIZED OXYGENATION OF IMIDAZOLES.

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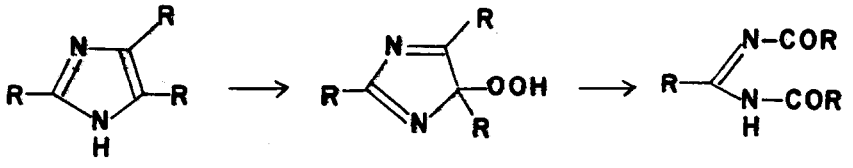
The reactions of imidazoles with singlet oxygen are of special interest in view of the probable involvement of the imidazole system in the photooxidative inactivation of certain enzymes. Thus, loss of biological activity during photooxidation of phosphoglucomutase[3], ribonuclease[4] and insulin[5], among other enzymes, has been correlated with the disappearance of histidine residues and, accordingly, with the oxidative destruction of imidazole rings.

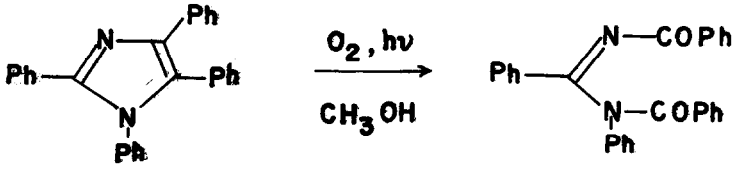
Earlier work[6,7,8] has shown that photooxidation of lophine (2,4,5-triphenylimidazole I, R=Ph) and derivatives leads to the formation of N,N'-diaroylbenzamidines (III) through hydroperoxides of structure II. We now wish to report studies on the photosensitized autoxidation of other imidazoles which provide further information regarding the structures of the peroxidic intermediates and the manner of their decomposition to isolable products.



I II III

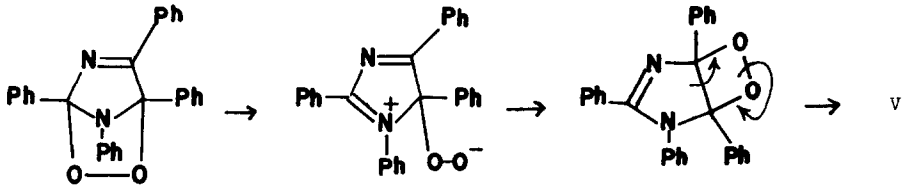
In the present work, the oxidations were run in dilute methanolic solution at room temperature using methylene blue as a sensitizer and a 150 watt floodlamp as the light source. Most of the reaction mixtures were worked up after 24 hr. of irradiation, except for the parent system, imidazole, which was relatively unreactive and required two weeks for the oxidation.

As was observed with triphenylimidazole (I, R=Ph), we found that tetraphenylimidazole (IV) underwent ready photooxidation to yield N,N'-dibenzoyl-N-phenylbenzamidine (V) (97%).[9]



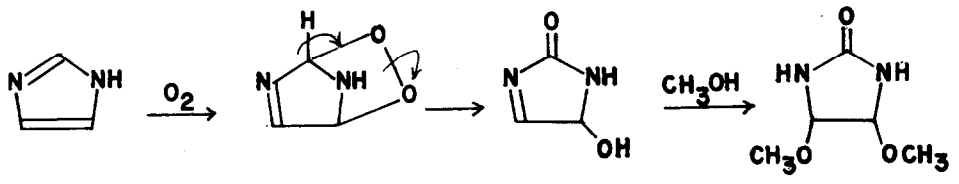
IV V

In this case a hydroperoxide corresponding to II cannot be an intermediate, although it is possible that a zwitterionic[10] counterpart, VIb, may be involved in the rearrangement of an initially formed transannular peroxide, VIa, through the sequence, VIa → VIb → VIc → V.[10a]



VIa VIb VIc

The parent heterocyclic system, imidazole, underwent slow photooxidation to yield a crystalline solid, m.p. 112-114°, $C_5H_{10}O_3N_2$ (30% crude), formulated as compound VII. The assignment of structure was based on the nmr spectrum showing three peaks in the ratio, 3:1:1 at τ 6.60 (singlet); 5.18 (singlet); 2.50 (broad singlet). Formation of VII has analogies in related photooxidations in the furan[11] and pyrrole[12] series whereby products are formed by an elimination reaction involving proton loss and cleavage of the O-O bond of the transannular peroxide.[13]



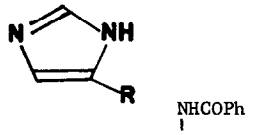
VII

We have also observed a similar type of conversion in the oxygenation of 4,5-diphenylimidazole, a reaction which yielded a mixture of products containing 5-methoxy-4,5-diphenylimidazolin-2-one (VIII) and 4,5-dimethoxy-4,5-diphenylimidazolidin-2-one (IX) as the principal components (45%).[14] N,N'-dibenzoylurea, a product of further oxidation, was formed in low yield (5%).

VIII IX

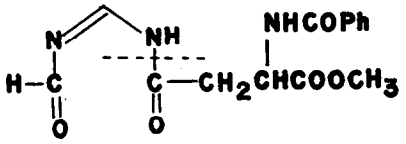
In order to learn more about the destruction by singlet oxygen of the histidine residue in enzyme systems, a model compound, N-benzoylhistidine methyl ester (Xa) was subjected to the above conditions of photosensitized oxygenation. The complex reaction mixture was not analyzed directly but was hydrolyzed in 6 N HCl and the solution thus obtained was examined for amino acids, according to the procedure of Spackman et.al.[15] The results

indicated that the reaction solution contained histidine (3%), aspartic acid[16] (62%), and unidentified products.



X_a, R = $CH_2CHCOOCH_3$ (NHCOPh)

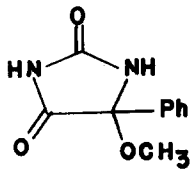
X_b, R = Ph



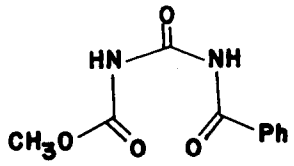
XI

Formation of aspartic acid in this sequence could perhaps be explained on the basis of an oxidation of Xa to XI, like the conversion of I to III, in which the imidazole ring is cleaved with development of a carbonyl group at the C-4 position. Hydrolysis of XI would then yield aspartic acid.

On the other hand, there is evidence[3,4,5] which indicates that the oxygenation of histidine is a more complex process, requiring more than one mole of oxygen per mole of substrate destroyed. In this connection, the reaction of 4-phenylimidazole (Xb) with oxygen under the above conditions is of interest. The state of oxidation of the isolated products, XII (15%) and XIII (2%) is clearly in line with the uptake of more than one mole of oxygen per mole of substrate. The hydantoin (XII), m.p. 167-170° was identified by the characteristic carbonyl infrared bands at 1792 and 1723 cm^{-1}, and by the nmr peaks at τ 6.63, 2.5 and 2.0. N-benzoyl-N'-carbomethoxyurea (XIII) was prepared independently by the reaction of benzoyl isocyanate with methyl carbamate in dry ether.



XII



XIII

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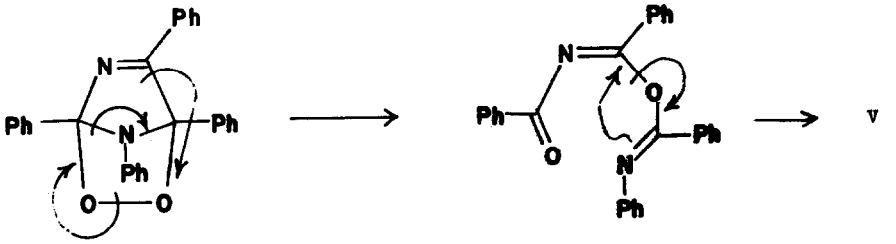

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