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SINGLET OXYGEN REACTIONS OF 2-CARBALKOXY-3-METHOXYPYRROLES.

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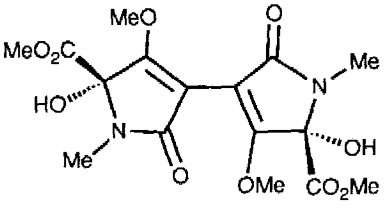
Abstract: The reactions of singlet oxygen with 3-methoxy-2-carbalkoxypyrroles lead to 2,5-oxygenation, 2,3-epoxides, or 2,3-oxidative cleavage, depending on substitution patterns and reaction conditions.

Among the heterocyclic systems which undergo reactions with singlet oxygen, furans, oxazoles and imidazoles have received considerable attention because the oxidation products have had application in organic synthesis.[1,2] Thus, there are a number of instances in which photooxidation of the furan ring has generated butenolides which have been incorporated into the framework of more complex molecules.[3] Likewise, oxazoles have been used as protecting-activating groups for carboxylic acids,[4] and imidazoles have been transformed by singlet oxygen to amino acid diamides and dipeptides.[5] On the other hand, very little use has been made of pyrrole photooxidation in synthesis, partly because the oxidation process normally takes place in low yields to give multiple products along with considerable decomposition.[6]

We have recently discovered a new method for forming 2-carbalkoxy-3-hydroxypyrroles in good yields by the reaction of primary amines with vinyl vicinal tricarbonyl compounds.[7] The ready availability of these systems and the likelihood of enhanced reactivity due to the electron-releasing substituents has prompted us to explore their reactions with singlet oxygen as a means of generating intermediates which could have application in synthesis. One such goal toward which we are working is the synthesis of the bis-unsaturated lactam **10** derived from the leaves and stems of the plant *Mercurialis leiocarpa*.[8] There is also special interest in the action of molecular oxygen on 3-methoxypyrroles since they occur as key components in the naturally-occurring prodigiosin pigments derived from bacterial sources,[9] as well as in bipyrroles recently isolated from marine sources.[10]



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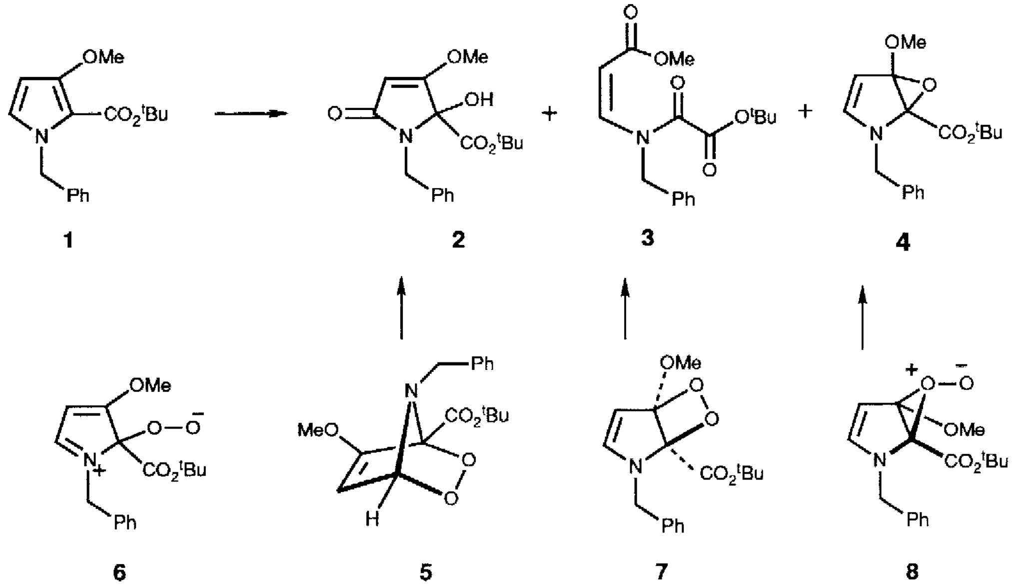
In general, pyrroles bearing electron-withdrawing substituents at the 2-position react sluggishly with singlet oxygen. Alkyl substitution increases the reactivity but the effect of a strongly electron-releasing 3-hydroxyl or 3-methoxyl substituent in the presence of a 2-carbalkoxy group has not been investigated. We now report that the tert-butyl ester of 2-carboxy-3-methoxy-N-benzylpyrrole **1** reacts rapidly with singlet oxygen. The photooxygenation was run in methanol at -15°C with methylene blue as sensitizer, a 650 watt Sylvania projector lamp as the light source, and water-cooling. The oxidation was complete in 4-5 minutes, yielding products **2** (45%), **3** (35%) and **4** (10%).

Scheme 1

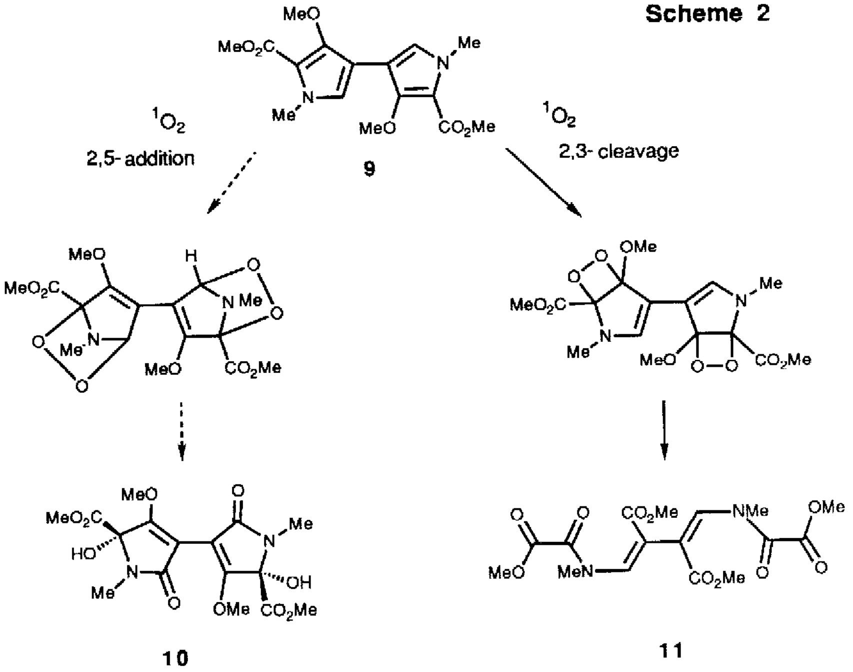


Formation of the hydroxy lactam **2** is in accord with the expected decomposition of an intermediate 2,5-transannular peroxide **5** by a β-elimination process as illustrated in Scheme 1. The intermediate **5** may be formed either by direct uptake of molecular oxygen or from the zwitterion **6**. Intermediate **6**, which may lead to **3** through the dioxetane **7**, could also be a precursor of epoxide **4** through the perepoxide **8**.

Support for the above reaction profile was found when a proton acceptor was added to facilitate the β-elimination. In the presence of 10% pyridine (-20°C, Rose Bengal), unsaturated hydroxy lactam **2** was formed in greatly enhanced yields (80%). Only 10-15% of the epoxide **4** and trace amounts of the 2,3-cleavage product **3** were formed concurrently. On the other hand, in the presence of a large excess of diphenyl sulfide,[11] capable of deoxygenating peroxy intermediates **6**,**7** or **8**, the 2,3-epoxide **4** was generated as the main product (56%) along with **2** as the minor product (36%).

In light of these results, we were interested in exploring the reaction of the dipyrrole **9**[12] with singlet oxygen as a possible route to the natural product recently isolated from *Mercurialis* *leiocarpa*, and shown by X-ray analysis to have the bis-lactam structure **10**. Uptake of oxygen by 2,5-addition would yield a bis-transannular peroxide which[13] could undergo peroxide cleavage (as in 5 to 2) to form the natural bis-lactam. Under all conditions of photooxygenation studied, including change of solvent from MeOH to CH_2Cl_2 or $CHCl_3$ and addition of pyridine or other bases, we isolated only the 2,3-cleavage product **11** (30%) Scheme 2. The structure of **11** was established by singlet crystal X-ray analysis (Figure 1).

Scheme 2



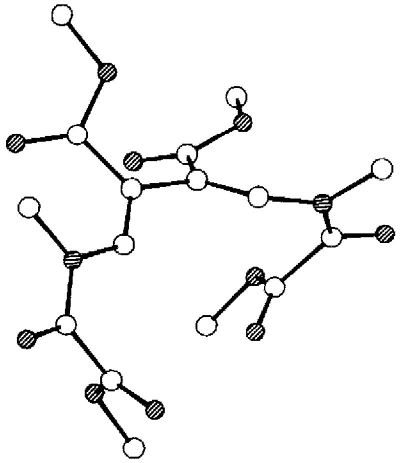
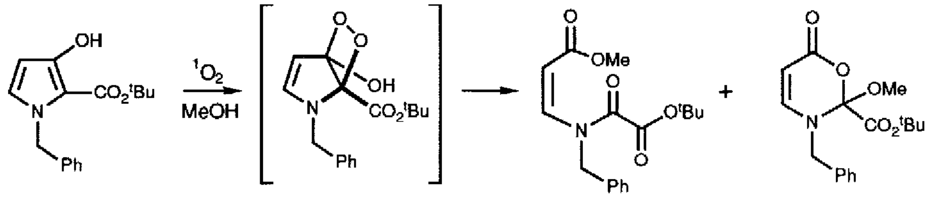


Figure 1. UPLOT drawing of **12** derived from photooxidation of **10**.

We are investigating this unusual result in order to learn more about the factors involved in 2,5-addition vs. 2,3-cleavage of this dipyrrole under the conditions of dye-sensitized photooxygenation.[14]

Reaction of the hydroxypyrrole **12** with singlet oxygen in methanol was complete in less than five minutes. In this oxidation, **12** appeared to react as the enol of a β-keto ester, giving products **3** and **3a** expected from 2,3-cleavage (70-80% for the mixture) (Scheme 3). None of the unsaturated lactam **2** resulting from 2,5-endoperoxide formation was observed.

Scheme 3



12 **3** **3a**

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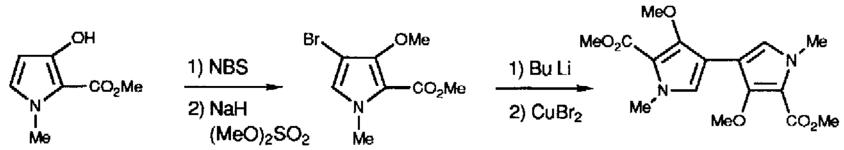
12. The dipyrrole **9** was synthesized by the procedure outlined below. V. Rotello, Ph.D. dissertation, Yale University 1989.



13. Assuming the favorable stereochemistry in the uptake of oxygen to form the 2,5-endoperoxide.
14. Foote has reported that changes of temperature and solvent can alter the course of the photooxygenation of 2-methoxy-3-methyl-cyclopenten-1-one where the substituents have opposing effects in reactivity toward singlet oxygen. Kwon, B.-M.; Foote, C.S. *J. Org. Chem.* **1989**, *54*, 3878.

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