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INTERMEDIATES IN THE REACTIONS OF OXAZOLES WITH SINGLET OXYGEN

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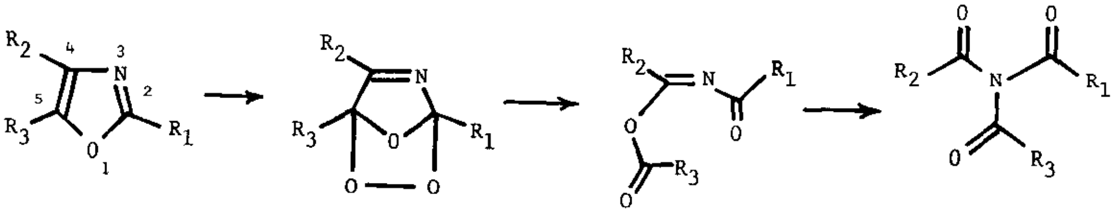
An intermediate peroxidic product in the photooxidation of an oxazole has been trapped by intramolecular nucleophilic attack of a carboxylate residue. Evidence is presented to support the view of the oxygenation as an initial 4+2 concerted addition of singlet oxygen yielding an endoperoxide.

Oxaxoles are among the most reactive heterocyclic systems toward singlet oxygen ($^1O_2$) and undergo a remarkable rearrangement to form triamides upon photooxidation. Earlier work,[1] including oxygen-18 tracer studies,[2] has favored a reaction pathway whereby initial uptake of $^1O_2$ yields an endoperoxide (1) which undergoes rearrangement to an imino anhydride (2). Subsequent O-acyl to N-acyl migration then yields the triamide, as outlined in Scheme I.



Scheme I 1 2 3

Under special conditions, as when R_2 and R_3 are part of a saturated ring, the O-acyl to N-acyl shift (2 → 3) does not occur for steric reasons, and the imino anhydride (2) may be isolated.[3] Alternatively, a solvent-dependent fragmentation of the endoperoxide may take place leading to nitriles.[4]

We now report that the endoperoxide (1) may be trapped by an intramolecular reaction with a carboxyl group. Thus, oxazole carboxylic acids of type (4) yield spirolactone hydroperoxides (7) upon photooxidation in chloroform at 0° (Table 1, Scheme II). The NMR spectra of the peroxides (7) show that 1:1 mixtures of the

Table 1 Spirolactones (7)

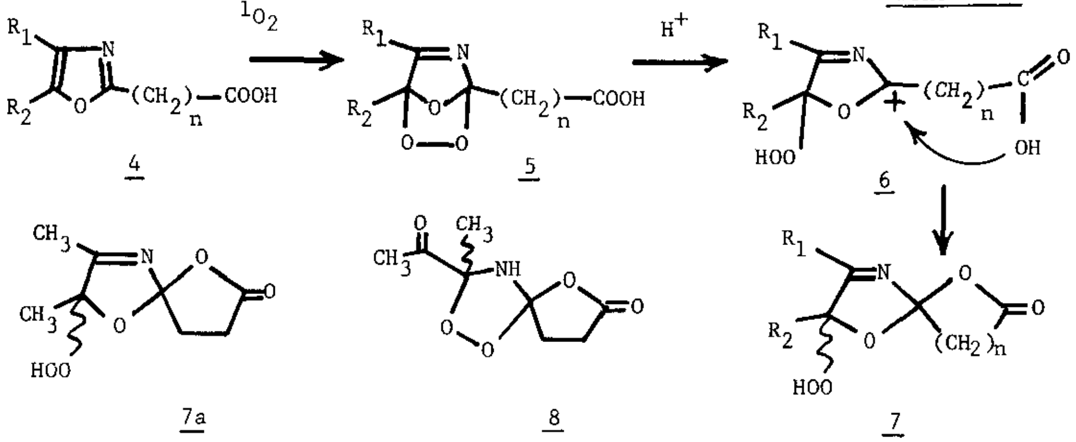
(7)	R_1	R_2	n	NMR (δ) Methyls	IR (cm^{-1})
a	CH_3	CH_3	2	1.52, 1.55; 2.19, 2.22	3150, 1780, 1680, 1440†
b	CH_3	CH_3	3	1.50, 1 55; 2.16, 2.19	3150, 1740, 1675, 1430
c	CH_3	Ph	2	2.05; 2.10	3200, 1800, 1680, 1460

† mp. 113°, dec. Anal. Calcd. for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.50; H, 5.36; N, 7.10.

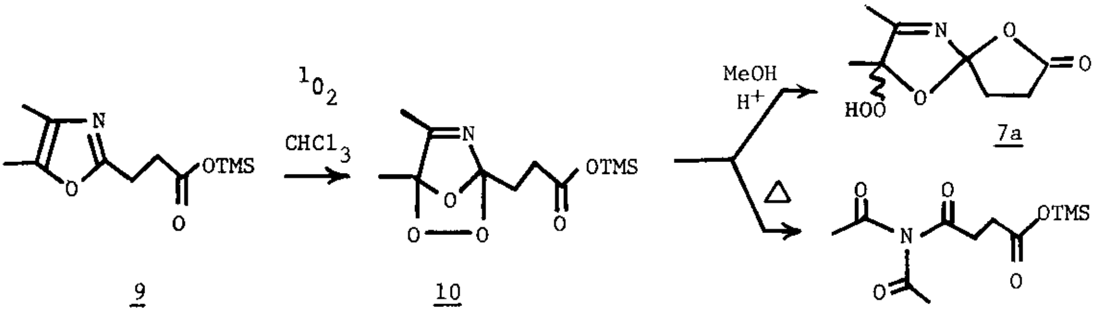
possible *diastereomers are* formed. In the case of peroxide (7a), a single diastereomer ($7a_1$) could be separated from the mixture ($7a_1$ and $7a_2$) by crystallization from chloroform. The substance, a solid, decomposing at 113°, gave a satisfactory *elemental analysis for* $C_8H_{11}NO_5$. The NMR spectrum (δ 1.52 (s, 3H), 2.19 (s, 3H), 2.41-2.82 (m, 4H), 8.7 (br. s, 1H)) and the infrared spectrum (peaks at 1780 and 1680 cm^{-1} corresponding to a 5-membered lactone and a cyclic imino group) are in complete agreement with the spirolactone structure ($7a_1$) assignable to one of the components of the diastereomeric mixture. An alternative structure (8)[9] would be expected to show an acyl carbonyl band around 1720 cm^{-1} and was therefore considered unlikely. Spirolactone ($7a_1$) underwent very slow change in solution to form the original 1.1 diastereomeric mixture (7a) plus some triamide.

The above evidence suggests that the endoperoxide (5), first formed, is converted to the carbonium ion (6) in an acid-catalyzed process. Intramolecular nucleophilic attack by the carboxyl group then leads to the mixture of diastereomers. Compound (7a) would be expected to revert to 6 under acid catalysis, but at a slower rate than the conversion of the unstable peroxide (5) to (6).

Scheme II



In the photooxygenation of the trimethylsilyl ester (9) we were able to observe reactions of the intermediate endoperoxide. Thus, 9 reacted with $^1O_2$ at 0° to yield peroxide (10), stable in solution at 0° (NMR δ 2.25 (s, 3H), 1.87 (s, 3H)). When treated with methanol, 10 underwent spirolactonization forming 7a as a 1:1 mixture of diastereomers, identical with the product formed from 4a (Scheme III). On warming to 25° the endoperoxide (10) rearranged to triamide (11) (NMR δ 2.37 (s, 6H)). Endoperoxides have also been observed as low-temperature intermediates in the photooxidation of imidazoles.[6]



Scheme III

Solvent and substituent effects indicate that the addition of $^1O_2$ to an oxazole is a concerted reaction. The β-value for 2,5-diphenyl-4-methyloxazole was determined in a variety of solvents (Table 2). (The β-value is equivalent to k_d/k_{rxn}, where k_d is the rate of decay of $^1O_2$ to $^3O_2$ in a solvent, and k_{rxn} is the rate at which the compound reacts with $^1O_2$ in the same solvent.) The very slight change in β-values in solvents of widely different polarity suggests that there is very little charge separation in the transition state for the $^1O_2$-oxazole reaction

Table 2. Solvent Effects

Solvent	$\beta \times 10^3$ M	$k_d \times 10^{-5} sec^{-1}$[7]	$k_{rxn} \times 10^{-7} M^{-1} sec^{-1}$	$\varepsilon^{25°}$
dioxane	1.75	0.29	1.61	2.21
benzene	2.04	0.80	3.92	2.28
n-amyl alcohol	3.01	-	-	13.9
ethanol	5.52	1.8	3.26	24.3
methanol	5.77	2.0	3.46	32.6
dimethyl sulfoxide	1.46	-	-	46.7

The above conclusion is supported by a study of substituent effects in the rates of reaction of 2-aryl-4-methyl-5-phenyloxazoles (12) with singlet oxygen (Table 3) A Hammett plot of these data shows a correlation with σ, and a ρ of -0.60. The small negative value of ρ is in accord with the electrophilic nature of $^1O_2$ and is consistent with very little charge development at the carbon-2 position of the oxazole in the transition state.[8]

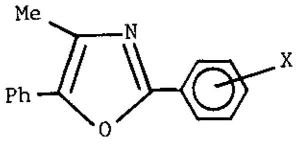


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Table 3. Hammett Data for Compound 12 in Methanol

Substituent	σ	$\beta \times 10^3$ M	log(β(H)/β(substituent))
p-OCH_3	-0.27	3.78	.18
p-CH_3	-0.17	5.34	.03
p-H	0	5 77	0
p-Cl	0.23	10.33	-.19
m-Cl	0.37	11.57	-.30
p-NO_2	0.78	16.64	-.46

ρ = -0 600 ± 0.003
correlation coefficient: 0.9834

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9. The dioxazole system has recently been reported by Scarpati and co-workers[5] as an intermediate in the photooxidation of 5-alkoxy oxazoles.

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