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(4+2)-CYCLOADDITION OF SINGLET OXYGEN TO OXAZOLES

FORMATION OF OXAZOLE ENDOPEROXIDES

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Singlet oxygen reacts with oxazoles $\underline{1a}-\underline{f}$ exclusively under (4+2)cycloaddition to yield the corresponding endoperoxides (secondary ozonides) 2a-f which were isolated and characterized at low temperatures.

In 1966, Wasserman and Floyd¹ showed that 2,4,5-triphenyloxazole yields tribenzamide when irradiated in methanol in the presence of oxygen and methylene blue as a sensitizer.

Ph
$$MB/h\nu$$

Ph $O_2/MeOH$ N(-C-Ph) 3

In spite of the fact that since then a great many of oxazoles have been studied as substrates of singlet oxygen $({}^{1}O_{2})$ reactions², there is only circumstantial evidence for the intermediate formation of oxazole endoperoxides (I)³. Possible pathways other than (4+2)-cycloadditions include (2+2)-cycloadditions to give 1,2-dioxetanes (II) and the formation of zwitterions (III) and perepoxides (IV); the latter are believed to be the precursors of 3H-1,2,4-dioxazoles (V)⁴.



None of these primary products with singlet oxygen should be stable at room temperature since only triamides were isolated from the reaction mixtures 2,5 .

We now wish to present evidence for the exclusive (4+2)-cycloaddition to various oxazoles <u>la-f</u> which carry hydrogen, methyl and/or phenyl groups as substituents. Oxazoles <u>la-e</u>, to the best of our knowledge not yet used as singlet oxygen acceptors, were chosen for this study because each of them contains an olefinic proton that should enable us to determine unequivocally the product structures by ¹³C NMR spectra analysis ⁶.

Oxazoles <u>la-f</u> consumed each one mole of oxygen when irradiated in the presence of a typical singlet oxygen photosensitizer such as tetraphenylporphin (TPP) in DCCl₂/CFCl₂ (1:3)

		3	3						
Compd.	R ²	R ⁴	R ⁵	¹³ C NMR (6, ppm)			¹ _H NMR (δ, ppm) ^a		
				C-2	C-4	C-5	R ²	R ⁴	R ⁵
<u>1a</u> 2a	н	снз	снз	148.7 (d) 110.2 (d)	130.1 (s) 176.3 (s)	143.4 (s) 107.9 (s)	7.63 6.91	2.01 2.31	2.16 1.97
<u>1b</u> 2b	СНЗ	Н	СНЗ	160.1 (s) 120.1 (s)	122.7 (d) 165.5 (d)	148.2 (s) 108.2 (s)	2.33 2.10	6.51 7.85	2.22 1.92
<u>1c</u> 2c	СНЗ	СНЗ	Н	161.1 (s) 120.4 (s)	136.3 (s) 174.1 (s)	134.0 (d) 100.6 (d)	2.22 2.05	2.06 2.31	7.14 6.16
<u>1d</u> 2d	СН _З	Н	Ph	160.9 (s) 121.2 (s)	121.4 (d) 164.3 (d)	151.1 (s) 109.3 (s)	2.48 2.16	b) 8.21	
<u>1e</u> 2e	Ph	Н	Ph	161.0 (s) 121.3 (s)	123.4 (d) 164.6 (d)	151.1 (s) 111.1 (s)		ь) 8.33	
<u>lf</u> <u>2f</u>	СНЗ	Ph	Ph	160.1 (s) 120.8 (s)	135.1 (s) 173.6 (s)	145.3 (s) 110.3 (s)	2.47 2.21		

Table 1. ¹³C and ¹H NMR Shifts of Oxazoles <u>1a-f</u> and Oxazole Endoperoxides <u>2a-f</u> in CDCl₂/CFCl₂ (1:3) at -50°C

a) all the ^{L}H NMR signals are singlets; b) chemical shift of the olefinic proton in the range where the protons of the phenyl groups (not shown in the Table) absorb.

or rose bengal (RB) in acetonitrile (MeCN) at temperatures below -50° C⁷. ¹H and ¹³C NMR spectra of the TPP/CDCl₃/CFCl₃ solutions were taken at -50° C immediately after the oxygen uptake ceased. These spectra are identical with those of the isolated colorless products <u>2a-f</u>, obtained from RB/MeCN solutions after solvent removal at -40° to -50° C/10⁻³ Torr, dilution of the residue with CDCl₃/CFCl₃ precooled to -50° C and flash filtration through silica gel at -40° C. No other ¹H and ¹³C NMR signals than those reported in Table 1 were observed.

Since the peroxidic products start to rearrange and/or to fragment in solution between -10°C and room temperature⁸ whereas the neat products tend to explode, elemental analyses and molecular weights could not be determined.

+ ¹0₂

In the 13 C NMR spectrum, the doublet at 148.7 ppm due to C-2 of <u>1a</u> is shifted upfield to 110.2 ppm in the product which is only compatible with structure I (<u>2a</u>) since structures II - V would require a doublet in the 150 ppm range as in the starting oxazole. The singlets of the methyl substituted C-atoms 4 and 5 of <u>1a</u> are shifted by about 40 ppm downfield and 35 ppm upfield to 176.3 and 107.9 ppm, respectively, as expected for <u>2a</u>. These shifts are incompatible with structures II and IV, for which upfield shifts for both singlets, i.e. of C-4 as well as of C-5, to the 110 ppm range would be expected. The carbonyl C-atom of structure V should exhibit a singlet in the 200 ppm range.

The doublets of C-4 of oxazoles <u>1b</u>, <u>1d</u> and <u>1e</u> are shifted from about 122 ppm to about 165 ppm in the corresponding products. These 43 ppm downfield shifts clearly indicate the formation of the ozonide structure I (<u>2b</u>, <u>2d</u> and <u>2e</u>, respectively). In contrast to these results, upfield shifts of the doublets should occur if one of the structures II through V would apply.

The doublet of C-5 of oxazole $\underline{1c}$ is shifted upfield by 33 ppm in accord with structures I, II and IV. However, the singlet of the methyl substituted C-4 of $\underline{1c}$ is shifted downfield by 38 ppm as is the singlet of the methyl substituted C-4 of $\underline{1a}$, indicating again that only structure I (2c) can be the structure of the peroxidic product.

Thus, transition from oxazoles $\underline{1a-e}$ to oxazole endoperoxides $\underline{2a-e}$ exhibit upfield shifts of 39 (±3) ppm for both the C-2 and the C-5 atoms and downfield shifts of 42 (±4) ppm for C-4, independent of whether these C-atoms are substituted by H, CH₃ or a phenyl group. If we apply the observed regularity of 13 C NMR chemical shift changes to the product obtained from oxazole <u>1f</u>, the singlets at 120.8, 173.6 and 110.3 ppm are easily attributed to C-2, C-4 and C-5, respectively, of the oxazole endoperoxide <u>2f</u>. It may be noted that we have also applied these empirical shift changes to a series of tri-substituted methyl and/or phenyl oxazoles ^{8,9} and found that the products obtained after reaction with singlet oxygen are in accord with endoperoxide structure I.

The ¹H NMR signals of the olefinic and methyl protons appear as singlets where they are expected to occur in endoperoxides $2\underline{a}-\underline{f}$. Thus, in comparison with the starting oxazoles, the olefinic protons are shifted upfield by 0.7 to 1 ppm, the protons of the methyl group by 0.2 to 0.3 ppm, if attached to C-2 and C-5; if attached to C-4, downfield shifts of similar amounts occur.

Kinetic results ⁹ indicate that oxazoles easily react with ${}^{1}O_{2}$ with rates comparable to those of the correspondingly substituted furans, i.e. in the range of $2 \cdot 10^{7}$ (<u>la</u>) to $0.2 \cdot 10^{7}$ M⁻¹ s⁻¹ (<u>le</u>), almost independent of the solvent used.

Finally, it seems to be interesting to report here our observation that 3-methylisoxazole (3), 1,2,5-oxadiazoles <u>4a</u> and <u>4b</u>, and 1,3,4-oxadiazoles <u>5a</u> and <u>5b</u> are apparently inert towards singlet oxygen since these compounds were recovered unaltered after irradiation in the presence of 0_2 and TPP in CHCl₃ or RB in MeCN for three to five hours at 13°C, during which no oxygen consumption occurred.



REFERENCES AND FOOTNOTES

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- 5. In case of 2-phenyl-4-methyl-5-methoxyoxazole, a dioxazole of structure V was isolated; it underwent a slow transformation to diacetyl benzamide ⁴.
- 6. 13 C and 1 H NMR spectra were taken on a Bruker WP-80-WC spectrometer using TMS as an internal standard.
- 7. A 25 ml irradiation unit with automatic oxygen consumption recording system (H.Paur, Dissertation, University of München, 1982) was used. The irradiation unit is a 25 ml flask surrounded by a cooling jacket through which an evacuated tube ("irradiation window") is fixed to the reaction vessel. Cooling, provided by using a LAUDA UK 60 SDW Ultrakryostat (+25°C to -60°C), leads to a thick layer of ice around the whole irradiation unit with the exception of the "irradiation window". A Hg high pressure lamp (Philips HP 125 W) was used as a light source; GG 14 glass (Schott, Mainz, 3 mm, cut-off at 490 nm) was placed between the "irradiation window" and the light source as a light filter. The solvents, $CDCl_3/CFCl_3$ (1:3) and acetonitrile, containing the sensitizers TPP and RB, respectively, at concentrations of $5 \cdot 10^{-4}$ M and the oxazoles at initial concentrations of $2 \cdot 10^{-1}$ M, were saturated with oxygen before irradiation; mixing the oxygen atmosphere with the solvents was executed by stirring (IKA-KMO-2, 1500 revol./min.).
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