

equipment, Dr. Larry Vickery for experimental assistance, and Professor J. B. Neilands for gifts of ferrichrome A.

References and Notes

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Polar Peroxidic Intermediates in Low Temperature Photooxygenation of *N*-Methylindoles¹

Sir

The reaction of singlet oxygen with enamines is of special interest in view of wide-spread involvement of the enamine grouping in many heterocyclic compounds.² Enamines are well known to react readily with singlet oxygen to form dioxetanes which can subsequently cleave to carbonyl and amide fragments.^{3,4} The 1,2-cycloaddition of singlet oxygen with electron-rich olefins like enol ethers or enamines had been assumed to be a concerted ($\pi_2s + \pi_2s$) or ($\pi_2s + \pi_2a$) process.⁵ However, recent theoretical calculations⁶ have predicted that the enamine-singlet oxygen reaction is a nonconcerted process involving a zwitterion as an initial intermediate, whereas the experimental evidence for the intermediacy of such dipolar peroxides is lacking.⁷ We now wish to report that low temperature photooxygenation of *N*-methylindoles gives a polar peroxide which is efficiently intercepted inter- and intramolecularly by alcohols and secondary amines, and that the trapping reactions show a remarkable temperature dependency.

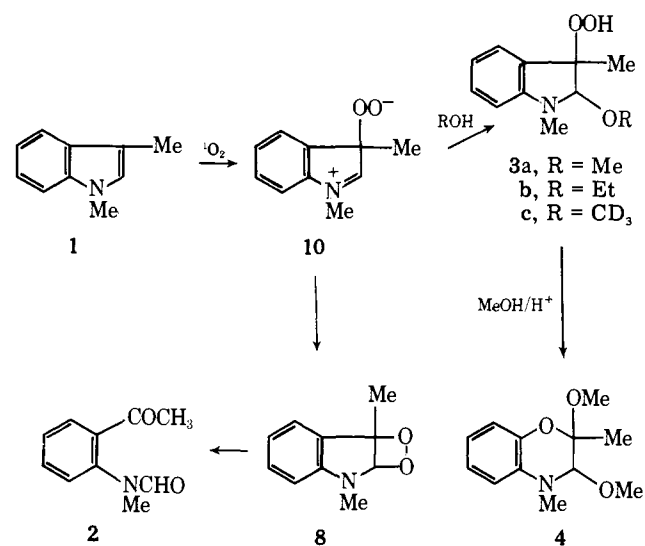
We previously reported that dye-sensitized photooxygenation of 3- or 2,3-substituted *N*-methylindoles such as 1,3-dimethylindole (**1**) at room temperature gives the normal C₂-C₃ ring cleavage products, **2**, in nearly quantitative yield.^{7c,8} However, rose bengal-sensitized photooxygenation⁹ of **1** (5 mM) at -70°C in methanol led to a slower but clean formation of the unstable 3-hydroperoxyindoline (**3a**) (97%) with a half-life of ca. 20 min at 30°C in CDCl₃.¹⁰ The structure of **3a**¹¹ was assigned on the basis of spectral data¹² and by converting it to benzoxazine **4**^{11,13} with methanol containing HCl.^{8a} Similar photooxygenation of **1** in ethanol at -70°C gave **3b**^{11,14} in quantitative yield. The overall reaction leading to **3** apparently consists of the addition of solvent alcohols to an initial intermediate, probably a polar peroxide.

Similar types of intramolecular trapping reactions have been observed with *N*-methyltryptophol (**5a**) and *N*_b-methoxycarbonyl-*N*_a-methyltryptamine (**5b**). As we reported earlier, photooxygenation of **5a** in methanol at -70°C produces **6a** (95%) and **7a** (3%), whereas at room temperature **5a** gives **7a**

Table I. Variation of the Product Distributions (**6**, **7**) with Temperature and Solvents^a

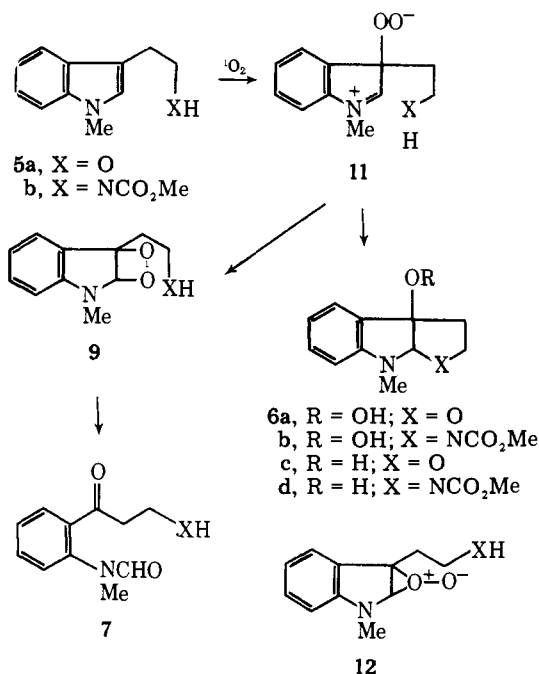
Compound	Solvent	Temp ($^\circ\text{C}$)	Products (%) ^b	
			6	7
5a	Methanol	20	— ^c	7a (95)
	Methanol	-35	6a (78)	7a (17)
	Methanol	-70	6a (95)	7a (3)
	Acetonitrile	20	— ^c	7a (85) ^d
	Acetonitrile	-30	6a (50)	7a (35)
	Acetone	20	6c (18)	7a (50) ^d
	Acetone	-70	6a (62)	7a (26)
	Methylene chloride ^e	20	6c (37)	7a (45) ^d
	Methylene chloride ^e	-70	6a (85)	— ^c
	5b	Methanol	20	6d (28)
Methanol		-70	6b (95)	— ^c
Acetonitrile		20	6d (36)	7b (55)
Acetonitrile		-30	6b (68)	7b (22)
Acetone		20	6d (51)	7b (36) ^d
Acetone		-70	6b (75) ^d	— ^c
Methylene chloride ^e		20	6d (32)	7b (35) ^d
Methylene chloride ^e		-70	6b (25) ^d	— ^c

^a Initial concentration (2 mM). Unless otherwise stated, rose bengal was used as a sensitizer (CuCl₂-CaCl₂ filter). ^b Determined by NMR analysis of the reaction mixture. Yields were based on reacted **5**. ^c **6** could not be detected. ^d Appreciable amounts of polymeric materials were formed. ^e Methylene blue (potassium chromate filter) was used as a sensitizer.



exclusively.^{8a} We also observed that the product ratio (**6/7**) is highly sensitive to the reaction temperature (Table I). The hydroperoxides **6a** and **6b** were not converted to **7a** and **7b**, respectively, under the conditions.¹⁵ As shown in Table I, the trapping reaction to yield **6** is taking place preferentially at low temperatures in any solvent listed in table I. A similar temperature dependency has also been observed in the photooxygenation of **5b**.¹⁶

These results clearly indicate that the initial intermediate is a peroxide which is capable of undergoing an efficient addition reaction with alcohols or secondary amines even at low temperature. Since dioxetanes including enamine dioxetanes⁴ are not known to react with nucleophiles such as alcohols or amines,¹⁸ it seems unlikely that the dioxetanes (**8**, **9**) are the intermediates.¹⁹ The results may most reasonably be explained



in terms of a stepwise mechanism involving a zwitterion (**10** or **11**), not by a concerted mechanism.²⁰ Thus the zwitterions (**10**, **11**) are intercepted by the nucleophiles at low temperatures to give the hydroperoxides (**3**, **6**) or rearrange to the dioxetanes (**8**, **9**) at ordinary temperature.²² According to the MINDO/3 calculations, the zwitterion, an initial intermediate in enamine-singlet oxygen reaction, has been predicted to undergo rearrangement to a dioxetane with a relatively high activation energy compared to that for other processes such as rearrangement to a perepoxide.^{6a} If so, it seems very likely that the lifetime of the zwitterions (**10**, **11**) will be longer at lower temperature, permitting the trapping reactions more efficiently. The product ratio (**6**/**7**) is also solvent dependent. Polar solvents appear to increase the ratio of the dioxetane mode products (**7**) to the trapping reaction at least at 20 °C (Table I), although the solvent effect is still obscure. It is known that polar solvents increase the ratio of dioxetane formation to ene reaction.^{21a,d,23}

In order to get the spectroscopic evidence for the initial intermediate, we carried out the photooxygenation of **5a** at -70 °C in an NMR cell. The NMR spectrum (-70 °C) of the reaction mixture in CD₃OD or CDCl₃ had only the resonances of **6a**. Neither zwitterion **11** nor dioxetane **9** could be detected at the temperature.²⁴ The spectroscopic studies at -70 °C provided no direct evidence in support of the zwitterions; however, we believe that the results described here may represent chemical evidence for the intermediacy of the zwitterionic peroxides.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education of Japan and the Japan Society for the Promotion of Science.

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- Irradiation was made with a tungsten-bromine lamp through an aqueous CuCl₂-CaCl₂ filter solution.
- The hydroperoxide **3a** readily decomposed in methanol with $\tau_{1/2}$ of ca. 15 min at 30 °C to give a complex mixture of products including **2** (30%) and polymeric materials.
- All new compounds gave satisfactory elemental analyses and mass spectral data.
- Viscous oil; starch-KI test positive; UV (EtOH) 245, 294 nm; NMR (CDCl₃) δ 1.58 (s, 3 H, Me), 2.90 (s, 3 H, NMe), 3.58 (s, 3 H, OMe), 4.45 (s, 1 H, NCHO), 6.30-7.40 (m, 4 H, arom H), 9.70 (s, OOH).
- Bp 110 °C/1 mmHg; UV (EtOH) 241 (log ϵ 3.57), 285 nm (log ϵ 3.20); NMR (CDCl₃) δ 1.60 (s, 3 H, Me), 3.18 (s, 3 H, NMe), 3.23 (s, 3 H, OMe), 3.35 (s, 3 H, OMe), 4.28 (s, 1 H, NCHO), 6.50-7.10 (m, 4 H, arom H).
- Viscous oil; starch-KI test positive; UV (EtOH) 247, 295 nm; NMR (CDCl₃) δ 1.30 (t, 3 H, J = 7 Hz, CH₂CH₃), 1.55 (s, 3 H, Me), 2.88 (s, 3 H, NMe), 3.80 (q, 2 H, J = 7 Hz, CH₂CH₃), 4.50 (s, 1 H, NCHO), 6.30-7.40 (m, 4 H, arom H), 9.65 (s, OOH).
- Brief refluxing or standing (1 h) at room temperature of the solutions of **6a** and **6b** gave **6c** and **6d**, respectively, in quantitative yield.
- Recently, Nakagawa et al.¹⁷ have reported the formation of **6b**, **6d**, and **7b** in the photooxygenation of **5b** in pyridine-methanol. The spectral data of **6b**, **6d**, and **7b** were identical with those obtained by the authors. We are indebted to Professors T. Hino and M. Nakagawa for disclosure of their results prior to publication.
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- The possibility that **3** and **6** are formed from the dioxetane **8** and **9**, respectively, cannot be ruled out completely, since the chemistry of indole dioxetanes has never been known. However, the temperature dependency and the solvent effect on the formation of **6** are not satisfactorily explained by the dioxetane mechanism, whereas the MINDO/3 calculations^{6a} have predicted that polar solvents increase the ratio of the rearrangement of zwitterion (**11**) to dioxetane (**9**) in accordance with the experimental results.
- Perepoxide such as **12** might also be proposed to explain the formation of **6a,b**. While perepoxides have been proposed to rearrange to ene products and/or dioxetanes,^{6a,21} there is no precedent in which perepoxides have been considered to react with alcohols or amines. Note that the compounds (**1**, **5**) having allylic hydrogens do not yield the ene products.
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- The NMR spectrum (-70 °C) of the reaction mixture resulting from the photooxygenation of **1** (CD₃OD, -70 °C) also showed the presence of **3c** as a sole product.

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Synthesis of Vane's Prostaglandin X, 6,9 α -Oxido-9 α ,15 α -dihydroxyprosta-(Z)5,(E)13-dienoic Acid

Sir:

Vane and co-workers have recently obtained evidence for the formation of a new and remarkably active prostaglandin, termed PGX, from the prostaglandin endoperoxides PGG₂ or PGH₂ and microsomal fractions of certain tissues, especially aorta, arterial wall, and fundus of stomach.^{1,2} Vane's PGX inhibits platelet aggregation as do PGE₁ and PGD₂, but is several times more potent; it also causes relaxation of arterial smooth muscle. Although no structure was proposed for PGX,