REACTION OF 3-METHYLINDOLE WITH SINGLET OXYGEN

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The photosensitized oxidation of indoles is of interest because of the involvement of tryptophyl residues in the photodynamic inactivation of some enzymes[1] and in the photo-yellowing of wool and silk, sensitized by fluorescent brightening agents (FBA's).[2,3] There are many data which indicate that electronically excited singlet-state oxygen is the reactive intermediate in the dye-sensitized photooxidation of many organic compounds. Much of these data consists of comparisons of the photooxidation product distributions with those obtained by reaction with singlet oxygen generated chemically by the reaction of hydrogen peroxide with sodium hypochlorite.[4]

Since singlet oxygen has been suggested as an intermediate in the dye-sensitized photodegradation of cotton and other fibres,[5,6] it seemed possible that singlet oxygen was the reactive intermediate in the FBA-sensitized photo-yellowing of wool and silk. As part of some studies to investigate this possibility, we needed to know the products from the reaction of singlet oxygen with tryptophyl residues in proteins and whether these products were formed in the FBA-photosensitized reaction.

This communication reports the reaction of singlet oxygen with a model for the tryptophyl residues in proteins, 3-methylindole. This compound was chosen rather than tryptophan or a tryptophyl peptide because of the comparative ease of separation and identification of the reaction products and because amino acid residues introduce complications not normally encountered in proteins.

Reaction of 3-methylindole with chemically generated singlet oxygen yielded two identifiable products, *o*-formamidoacetophenone (1) and *o*-aminoacetophenone (2), in yields of 16% and 7% respectively. Similar yields of these compounds were obtained from the eosin-sensitized photooxidation of 3-methylindole, providing evidence that singlet oxygen is an intermediate in this photooxidation. No evidence could be obtained for the presence of the known 3-methylindole oxidation products, 3-methyloxindole and 3-methyldioxindole. The latter was expected because dioxindolylalanine has been claimed as a product of the dye-sensitized photooxidation of tryptophan.[7]

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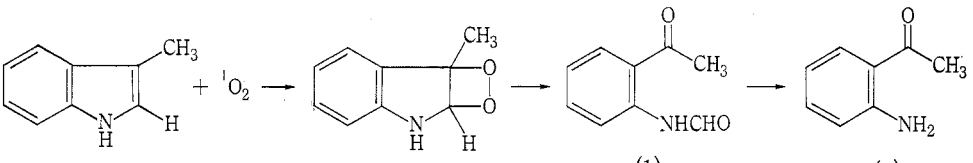
Considerable evidence has been obtained to show that singlet oxygen reacts with alkenes activated by amino or alkoxy groups to yield dioxetans, which decompose thermally to yield carbonyl compounds.[8,9] Thus, a likely mechanism for the formation of *o*-formamidoacetophenone (1) from the reaction of singlet oxygen with 3-methylindole involves, as an intermediate, the dioxetan (3). *o*-Aminoacetophenone would be readily obtained from its formyl derivative by hydrolysis during the work-up.



(3) (1) (2)

When a solution containing 3-methylindole and an FBA, the sodium salt of 1,3-diphenylpyrazoline-4′-sulphonic acid (4), was irradiated under conditions where the FBA absorbed the majority (>99%) of the radiation, complete photodegradation of 3-methylindole was effected in 3 days. No evidence could be obtained for the formation of the products of attack by singlet oxygen, which suggests that the FBA (4) does not sensitize the formation of singlet oxygen.

Experimental

The following compounds were commercial samples: eosin (G. T. Gurr), *o*-aminoacetophenone (Fluka), 3-methylindole (L. Light), purified before use by crystallization from light petroleum.

The following compounds were synthesized by literature methods: *o*-formamidoacetophenone,[10] m.p. 76–77° (lit.[11] 78°), *o*-acetamidoacetophenone,[12] m.p. 73–74° (lit.[12] 76–77°), 3-methyloxindole,[13] m.p. 120° (lit.[13] 121–122°), 3-methyldioxindole,[14] m.p. 161–163° (lit.[14] 161–162°).

The pyrazoline FBA (4) was synthesized in these Laboratories by G. C. Ramsay.

Irradiations

Solutions were irradiated in Pyrex containers with a 400-W Sylvania Metalarc lamp. This lamp emits visible and ultraviolet radiation with a cutoff at 310 nm. Air was bubbled through the solutions which were cooled by a water-filled glass coil.

Reaction of 3-Methylindole with Hypochlorite–Hydrogen Peroxide

A solution of 3-methylindole (1·31 g, 10 mmol) in methanol (50 ml) was cooled to 0°C and 100-volume hydrogen peroxide (3 ml) was added. A solution of sodium hypochlorite (0·62M, 40 ml) was added dropwise with stirring and cooling during 60 min, care being taken to keep the

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tip of the dropping funnel beneath the surface of the methanol solution. Methanol was then removed under vacuum at room temperature and the resulting mixture extracted with ether; the extract was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was adsorbed onto silica gel for chromatography. Elution with benzene yielded starting material (430 mg) followed by *o*-aminoacetophenone (67 mg, 7%), which was identified by comparison (infrared spectrum, melting point, mixed melting point) of its acetyl derivative with authentic material. Elution with a mixture of benzene and chloroform (19:1) yielded *o*-formamidoacetophenone (173 mg, 16%), m.p. 76–77°, identical (melting point, mixed melting point, infrared) with authentic material. Elution with increasing proportions of oform in benzene and then with chloroform yielded intractable brown solids (total weight 640 mg).

Dye-Sensitized Photooxidation of 3-Methylindole

A solution of eosin (65 mg) and 3-methylindole (1·31 g) in methanol (1400 ml) was irradiated for 14 hr. The solvent was then removed under reduced pressure and the residue chromatographed as described above. 3-Methylindole (92 mg), *o*-aminoacetophenone (120 mg, 10%), and *o*-formamidoacetophenone (238 mg, 16%) were isolated and identified as before.

FBA *Photosensitization of 3-Methylindole*

A solution of the diphenylpyrazoline (4) (0·20 g) and 3-methylindole (0·50 g) in methanol–water (5:1) (600 ml) was irradiated for 3 days. The solvent was then removed under reduced pressure and the chloroform-soluble fraction of the residue was chromatographed on silica gel as before. The eluted fractions were scanned for *o*-aminoacetophenone and *o*-formamidoacetophenone using thin-layer chromatography on silica gel with diisopropyl ether as solvent. In this system 3-methylindole had R_F 0·60, *o*-aminoacetophenone R_F 0·50, and *o*-formamidoacetophenone R_F 0·25. No evidence for the presence of any of these compounds could be obtained. No pure compound could be isolated from any of the fractions.

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