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Dye-Sensitized Photooxygenation of Isoniazid by Singlet Oxygen

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Dye-sensitized photooxygenation of isoniazid has been carried out. The product has been isolated and characterized. The participation of singlet oxygen as the active oxidizing species has also been confirmed. A tentative mechanism for the photooxygenation of isoniazid by singlet oxygen has been proposed.

INTRODUCTION

A great deal of the literature survey reveals that oxidation of heterocycles has been extensively investigated[1-10], however, little attention has been received by pyridine and its derivatives in this regard[11-14]. Isoniazid, a pyridine derivative, is commonly used as antituberculosis drug and it is necessary to know the fate of oxidation of isoniazid by singlet oxygen and, therefore, the present work was undertaken.

EXPERIMENTAL

Isoniazid (BDH) was purified by recrystallisation from ethanol. The methylene blue (CI 52015, Aldrich) was used as received. Solvents were dried and distilled before use. Doubly distilled water was used to prepare all solutions.

All the reactions were carried out in a corning vessel of capacity 500 ml. A 500 W tungsten lamp (Sylvania) was used in all the experiments for irradiation. An aerator was used for bubbling air through the solution. Air served two functions of (i) generating singlet oxygen in the presence of the sensitizer and light; (ii) continuous stirring of the reaction mixture.

Electronic absorption spectrum was recorded on Backman Model 26. Infra-red spectrum was scanned on Perkin-Elmer Grating 377 infrared spectrophotometer in KBr pallet. NMR was recorded with 90 MHz ET FX 600 JEOL. Mass spectrum was recorded on JEOL DX 300 with JMA 2000 data processing system.

Isoniazid (2.0 g) was dissolved in 250 ml of distilled water, 2 ml aqueous solution of methylene blue (1.0×10^{-3} M) was added to this solution so that the concentration of methylene blue in the reaction mixture was 8.0×10^{-6} M. The reaction mixture was exposed to light with

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a tungsten lamp kept at a distance of 20 cms from the lower surface of the reaction flask. Simultaneously air was bubbled in the reaction mixture. The reaction mixture showed the formation of an amorphous compound after 60 hrs of irradiation. This compound was separated from the reaction mixture by vacuum filtration. The dye adsorbed on the solid compound was removed by the addition of activated charcoal. The product was recrystallized from hot water and acetone mixture (1 : 1, v/v) (white crystals, m.pt. 258°C, yield 0.80 g).

Elemental analysis: Calculated for $C_6H_5N_3O_3$: C 43.11, H 2.99 and N 25.14%; found: C 43.01, H 2.75 and N 25.03%.

u.v. λ_{max} *(in methanol)*: 212 and 262 nm.

i.r. ν_{max} *(KBr)*: 3420(s), 2960–70(s), 1950–60(s), 1690(s), 1685(s), 1660(s), 1600(m), 1540(w), 1495(s), 1420(m), 1300(m), 1130(s), 1060(m), 940(m), 850(m), 740(s), 690(s) and 680(s) cm^{-1}.

n.m.r. τ: 8.52 [2H, S (broad)], 4.10 (1H, s broad], 2.82 [1H, d] and 2.64 [1H, d].

mass m/e (I%): 167 (20.8), 149 (46.4), 101 (14.48), 79 (9.8), 77 (29.6), 76 (8.4), 73 (8.8), 71 (20.0), 69 (32.8), 67 (14.4), 65 (39.2), 60 (20.8), 54 (100), 53 (19.2) and 52 (8.8).

Controlled experiments were also carried out in the absence of light or dye or air and it was observed that no product was formed. This observation confirms that all these three components, light, air and dye, are necessary for the oxidation of isoniazid.

The participation of singlet oxygen in the reaction was confirmed by using different singlet oxygen scavengers, *e.g.*, DABCO, β-carotene, nickel chloride, α-tocopherol etc. The yield of product was found to decrease considerably in their presence suggesting that singlet oxygen is the active oxidizing species in the photooxidation of isoniazid. The results are reported in Table 1.

TABLE 1

[Methylene blue] = 8.0×10^{-6} M
[Scavenger] = 1.0×10^{-5} M

Scavenger	Yield of the product (%)
—	40.0
1,4-Diazabicyclo-2,2,2-octane [DABCO]	Nil
β-carotene	Nil
Nickel chloride	0.5
Cobalt chloride	0.8

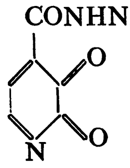
RESULTS AND DISCUSSION

The electronic absorption spectrum of the product shows two bands at (i) 212 nm, characteristics of an amide group and (ii) 262 nm, indicating the presence of a carbonyl group attached to some ring system.

The infra-red spectrum indicates that aromatic nature of the isoniazid has been lost since the bands in the region 3000–3100 cm^{-1} were found absent. The presence of an absorption band at 1660 cm^{-1} may be assigned to monosubstituted amide —CO—NH—. The band at 3420 cm^{-1} indicates secondary N—H stretching vibrations of amide group. The free —NH$_2$ group has been confirmed by the presence of N—H bending vibrations in the region of 1650–1560 cm^{-1}. The absorption at 690 cm^{-1} indicates the C—H bending vibrations of a disubstituted alkene. The bands at 1685 and 1690 cm^{-1} may be attributed to C—N stretching vibrations.

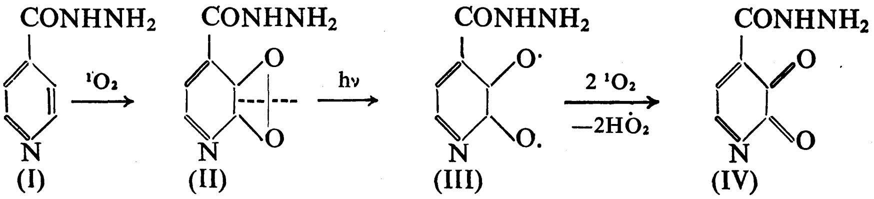
The broad singlets at 8.52 τ and 4.10 τ indicates the presence of —NH$_2$ and —CONH— groups. The doublets at 2.82 τ and 2.64 τ indicate the aromatic —CH adjacent to the $>$C—CONHNH$_2$ and to the nitrogen, respectively. The molecular ion peak has been observed at m/e = 167. This gives a fragment at m/e = 149 on dehydration, followed by cyclization. The base peak was observed at m/e = 54 and it may be assigned to the fragment [C=N—CO]$^+$. The other fragments are characteristic of a diketone.

Thus on the basis of analytical and spectral data, the product has been assigned the following structure.



The following tentative mechanism has been proposed for the photooxygenation of isoniazid by singlet oxygen. The dye is excited to its triplet state by the absorption of light and in turn excites the ground state oxygen to its first excited state. So formed, singlet oxygen ($^1O_2$) then reacts with isoniazid (I) to give corresponding dioxetane (II). The dioxetane then undergoes homolytic fission at O—O bond to give diredical (III)[15] which on hydrogen abstraction by singlet oxygen will give the product (IV).

Isoniazid may also form other dioxetanes by the attack of singlet oxygen on other C=C and C=N bonds but from these dioxetanes, formation of product could not be explained.



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