OXIDATIVE TRANSFORMATION OF TRYPTOPHAN TO 5-HYDROXY-N'-FORMYLKYNURENINE

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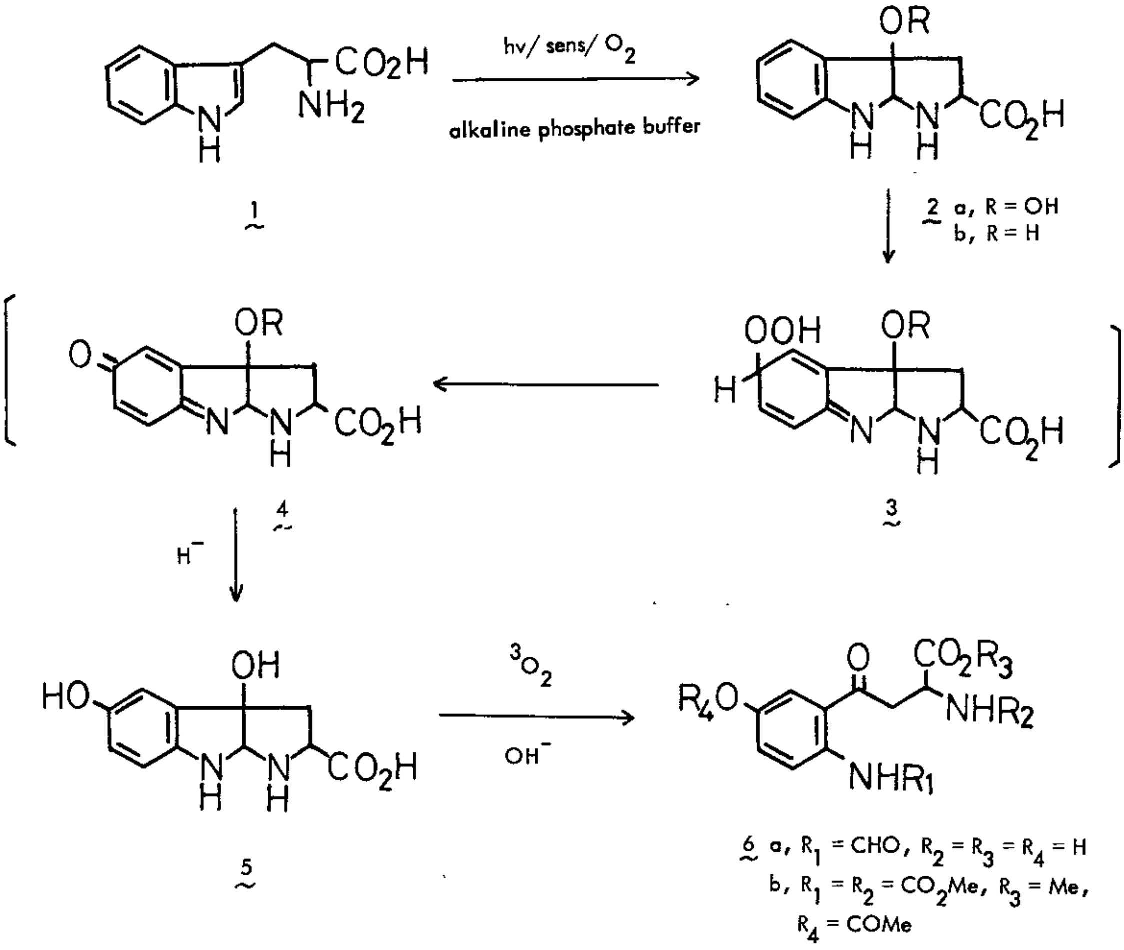
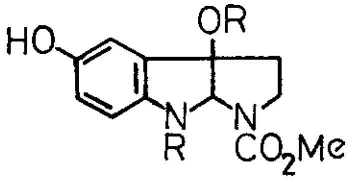
Abstract — Dye-sensitized photooxygenation of L-tryptophan in an alkaline phosphate buffer followed by $NaBH_4$ reduction afforded 3a,5-dihydroxypyrroloindole 5 which readily underwent air oxidation to give 5-hydroxy-N'-formylkynurenine 6a.

We had earlier shown[1] that the dye-sensitized photooxygenation of tryptophan gave the hydroperoxide 2a as the main product in the wide range of pH (2.7-8.9) and N'-formylkynurenine was formed as the major product in sodium carbonate-acetic acid solution.

We have now isolated and characterized a new reaction product, 5-hydroxy-N'-formylkynurenine 6a by further examination of dye-sensitized photooxygenation of L-tryptophan in alkaline phosphate buffers. L-tryptophan 1 (500 mg) was irradiated[2] for 1.5 h at 0-5°C in the presence of methylene blue (MB) (1/50-1/100 mol equiv) under a stream of O_2 in phosphate buffer (300 ml, pH 7.7)[3]. The reaction mixture was then treated with Me_2S and left overnight followed by ion exchange column chromatography. Lyophilization of the elution with water provided 5-hydroxy-N'-formylkynurenine 6a, $[\alpha]_D^{11}$ $-41.3°$ (c = 1, H_2O), λmax (H_2O) 234, 261sh, 347 nm in 24% yield, together with 2b in 16% yield and a small amount of N'-formylkynurenine. The structure of 6a was further confirmed by its conversion into the acylated derivative 6b[4], mp 141.5-142.5°C, $[\alpha]_D^{19}$ $+15°$ (c = 0.25, EtOH). The UV spectrum of the reaction mixture showed a maximum at 269 nm (in H_2O) reminiscent of a typical quinoneimine chromophore[5], suggesting that the quinoneimine 4 would be an intermediate.

Accordingly, when the reaction mixture was reduced with $NaBH_4$ under N_2 followed by immediate neutralization with dil HCl and work-up, 3a,5-dihydroxypyrroloindole 5 was obtained in 95% yield as a mixture of cis and trans isomers[1c], almost colorless powder, mp 199-201°C (dec.) ; λmax (H_2O) 238, 312 nm ; λmax (H_2O-OH^-) 243, 326 nm and 6a was not isolated. However, in contrast to 2b, 5 was found to be very unstable under basic conditions and suffered immediate aerial oxidation to 6a. Consequently, without isolating 5, treatment of the $NaBH_4$ reduction mixture with oxygen for 2 h at room temperature improved the yield of 6a up to 44% from 1.


hν/ sens/ O_2
alkaline phosphate buffer
1
2 a, R = OH
b, R = H
3
4
H^-
5
$^3O_2$
OH^-
6 a, R_1 = CHO, R_2 = R_3 = R_4 = H
b, R_1 = R_2 = CO_2Me, R_3 = Me,
R_4 = COMe



7 a, R = H
b, R = Ac

The similar oxygenation of N$'$-formylkynurenine did not proceed and recovered unchanged. On the other hand, **2a** and **2b** were converted to **6a** in 42% and 16% yields, respectively under the similar conditions, whereas in the absence of MB **2a** and **2b** were not oxidized to **6a**.

Formation of **5** might be explained by the initial hydroperoxidation of para-position of the primary product **2** by dye-sensitized photooxygenation in alkaline phosphate buffer to give the quinoneimine **4** via **3** which was converted to **5** on treatment with $NaBH_4$ as shown in the Scheme. The mechanism of oxidation of **5** to **6** is not clear but may well involve the initial oxidation of the phenolate anion of **5** since **5** is quite stable in neutral media.

Further support that the benzene ring oxidation can occur in the dye-sensitized photooxygenation was obtained by the reaction of N_b-methoxycarbonyltryptamine in the similar condition[7] to give 3a,5-dihydroxy-1-methoxycarbonylpyrroloindole **7a** which was identified as its 3a,8-diacetate **7b**[8] in 54% yield. However, 1-methoxycarbonyl derivative **7a** is stable to air oxidation in alkaline phosphate buffer and was not converted to 5-hydroxy-N$'$-formylkynurenine derivative.

These results appear to provide a new example of oxidation of aniline derivatives to quinoneimines by dye-sensitized photooxygenation.

ACKNOWLEDGEMENT

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REFERENCES AND NOTES

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2. Aqueous $K_2Cr_2O_7$ was used as a liquid filter.
3. The buffer contained EtOH (5%). **6a** was obtained in 17% yield at pH 8.4.
4. **6b** : λmax (EtOH) nm (ϵ) 231 (34800), 256 (11700), 262 (10600), 338 (4790) ; ν max (KBr) cm^{-1} 3325, 1774, 1747, 1734, 1700, 1672, 1665, 1530 ; δ ($CDCl_3$, 270 MHz) 2.32 (s, 3H, CH_3CO_2), 3.50 - 4.00 (m, 2H, CH_2), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 3.76 (s, 3H, $NHCO_2C\underline{H}_3$), 3.79 (s, 3H, $NHCO_2C\underline{H}_3$), 4.73 (m, 1H, $NH\text{-}C\underline{H}CO_2CH_3$), 5.74 (d, 1H, J = 8.6 Hz, $N\underline{H}\text{-}CHCO_2CH_3$, exchange-

able), 7.31 (dd, 1H, J = 2.4 and 9.2 Hz, C_4-H), 7.58 (d, 1H, J = 2.4 Hz, C_6-H), 8.53 (d, 1H, J = 9.2 Hz, C_3-H), 10.86 (s, 1H, NH) ; m/z 396 (6) M^+, 162 (100).

5. T. Hino, M. Taniguchi, and M. Nakagawa, Heterocycles, 1981, **15**, 187.

6. The ratio of the cis- and trans-isomers **5** was estimated as 7 : 3 by the ^{1}H-NMR spectrum : δ (D_2O, 270 MHz) 3.89 (dd, 0.7H, J = 6.9 and 11.7 Hz, cis C_2-H), 4.35 (m, 0.3H, trans C_2-H), 5.32 (d, 0.3H, J = 5.9 Hz, trans C_{8a}-H), 5.40 (s, 0.7H, cis C_{8a}-H). See also reference **1c**.

7. The buffer contained EtOH (10%).

8. **7b** : mp 172-173°C (MeOH), λmax (95% EtOH) nm (ε) 247 (14500), 282 (1770) ; νmax (KBr) cm^{-1} 3308, 1767, 1712, 1655 ; δ ($CDCl_3$, 270 MHz) 2.10 (s, 3H, OAc), 2.29 (s, 3H, NAc), 2.39 (m, 2H, CH_2), 2.80 - 2.95 (m, 2H, CH_2N), 3.67 (s, 3H, CO_2Me), 4.80 (broad s, 1H, OH), 5.65 (s, 1H, NCHN), 7.03 (dd, 1H, J = 8.9 and 2.6 Hz, C_6-H), 7.15 (d, 1H, J = 2.6 Hz, C_4-H), 7.89 (d, 1H, J = 8.9 Hz, C_7-H) ; m/z 334 (9) M^+, 250 (100).

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