

OXIDATIVE TRANSFORMATION OF TRYPTOPHAN TO 5-HYDROXY-N¹-FORMYLKYNURENINE

Masako Nakagawa, * Yukio Yokoyama, Shiro Kato, and Tohru Hino

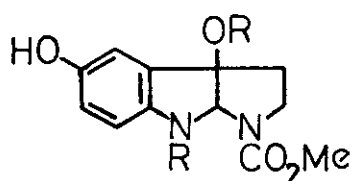
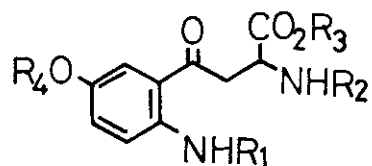
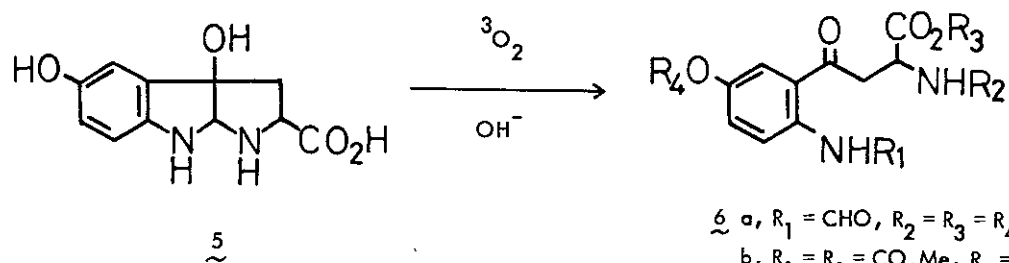
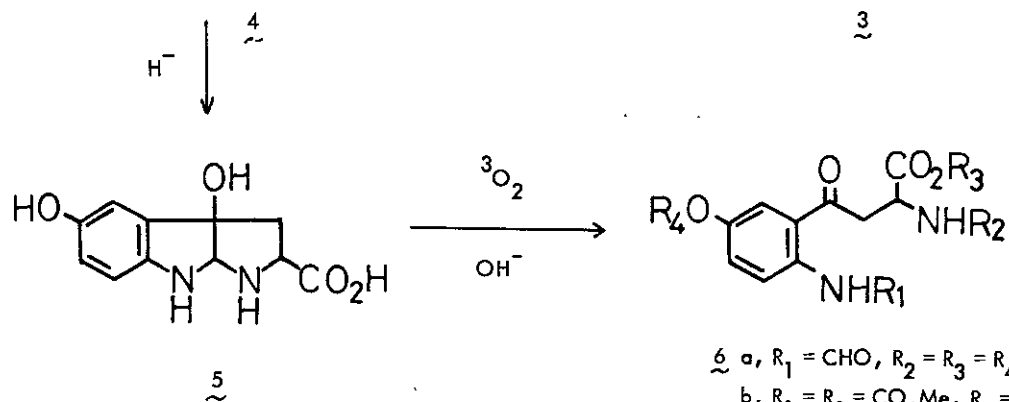
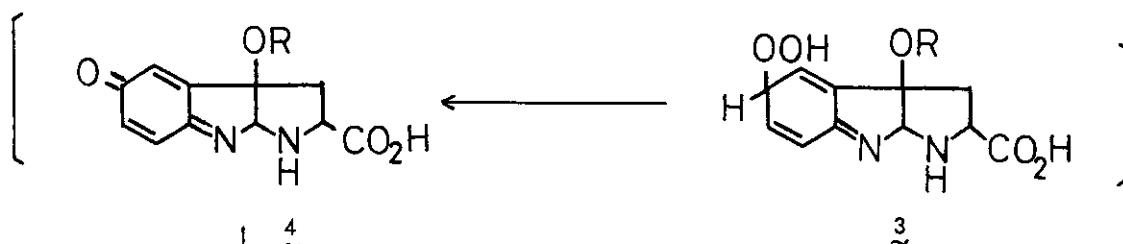
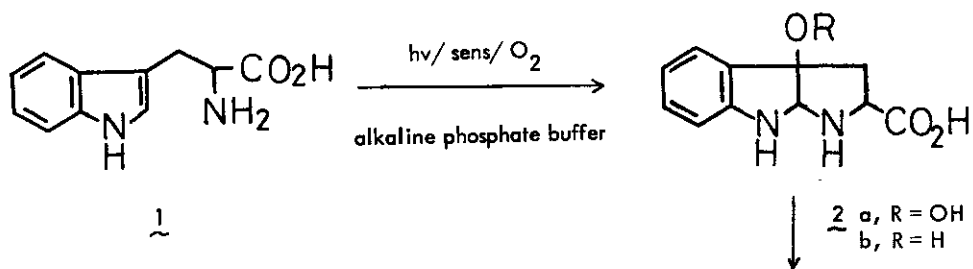
Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Chiba-shi, 260, Japan

Abstract — Dye-sensitized photooxygenation of L-tryptophan in an alkaline phosphate buffer followed by NaBH₄ reduction afforded 3a,5-dihydroxypyrrroloindole 5 which readily underwent air oxidation to give 5-hydroxy-N¹-formylkynurenine 6a.

We had earlier shown¹ 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 N¹-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-N¹-formylkynurenine 6a by further examination of dye-sensitized photooxygenation of L-tryptophan in alkaline phosphate buffers. L-tryptophan 1 (500 mg) was irradiated² 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 O₂ in phosphate buffer (300 ml, pH 7.7)³. The reaction mixture was then treated with Me₂S and left overnight followed by ion exchange column chromatography. Lyophilization of the elution with water provided 5-hydroxy-N¹-formylkynurenine 6a, [α]_D¹¹ -41.3° (c = 1, H₂O), λ_{max} (H₂O) 234, 261sh, 347 nm in 24% yield, together with 2b in 16% yield and a small amount of N¹-formylkynurenine. The structure of 6a was further confirmed by its conversion into the acylated derivative 6b⁴, mp 141.5-142.5°C, [α]_D¹⁹ +15° (c = 0.25, EtOH). The UV spectrum of the reaction mixture showed a maximum at 269 nm (in H₂O) reminiscent of a typical quinoneimine chromophore⁵, suggesting that the quinoneimine 4 would be an intermediate.

Accordingly, when the reaction mixture was reduced with NaBH₄ under N₂ followed by immediate neutralization with dil HCl and work-up, 3a,5-dihydroxypyrrroloindole 5 was obtained in 95% yield as a mixture of *cis* and *trans* isomers^{1c}, almost colorless powder, mp 199-201°C (dec.) ; λ_{max} (H₂O) 238, 312 nm ; λ_{max} (H₂O-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 NaBH₄ reduction mixture with oxygen for 2 h at room temperature improved the yield of 6a up to 44% from 1.



The similar oxygenation of N¹-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 NaBH₄ 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 condition⁷ to give 3a,5-dihydroxy-1-methoxycarbonylpyrroloindole 7a which was identified as its 3a,8-diacetate 7b⁸ in 54% yield. However, 1-methoxycarbonyl derivative 7a is stable to air oxidation in alkaline phosphate buffer and was not converted to 5-hydroxy-N¹-formylkynurenine derivative.

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

ACKNOWLEDGEMENT

We thank the Ministry of Education, Science, and Culture, Japan for financial support of the research.

REFERENCES AND NOTES

- (a) M. Nakagawa, H. Watanabe, S. Kodato, H. Okajima, T. Hino, J.L. Flippen, and B. Witkop, Proc.Natl.Acad.Sci., USA, 1977, 74, 4730; (b) M. Nakagawa, S. Kato, S. Kataoka, and T. Hino, J.Am.Chem.Soc., 1979, 101, 3136; (c) M. Nakagawa, S. Kato, S. Kataoka, S. Kodato, H. Watanabe, H. Okajima, T. Hino, and B. Witkop, Chem.Pharm.Bull., 1981, 29, 1013; (d) M. Nakagawa, S. Kato, K. Nakano, and T. Hino, J.C.S.Chem.Comm., 1981, 855.
- Aqueous K₂Cr₂O₇ was used as a liquid filter.
- The buffer contained EtOH (5%). 6a was obtained in 17% yield at pH 8.4.
- 6b: λ_{max} (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 (CDCl₃, 270 MHz) 2.32 (s, 3H, CH₃CO₂), 3.50 - 4.00 (m, 2H, CH₂), 3.69 (s, 3H, CO₂CH₃), 3.76 (s, 3H, NHCO₂CH₃), 3.79 (s, 3H, NHCO₂CH₃), 4.73 (m, 1H, NH-CHCO₂CH₃), 5.74 (d, 1H, J = 8.6 Hz, NH-CHCO₂CH₃, 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 1H -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), λ_{max} (95% EtOH) nm (ϵ) 247 (14500), 282 (1770); ν_{max} (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).

Received, 19th September, 1983