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PHOTOCHEMICAL OXIDATIVE C_α-C_β BOND CLEAVAGE OF TRYPTOPHAN SIDE-CHAIN BY PYRIMIDO[5,4-g]PTERIDINE N-OXIDE

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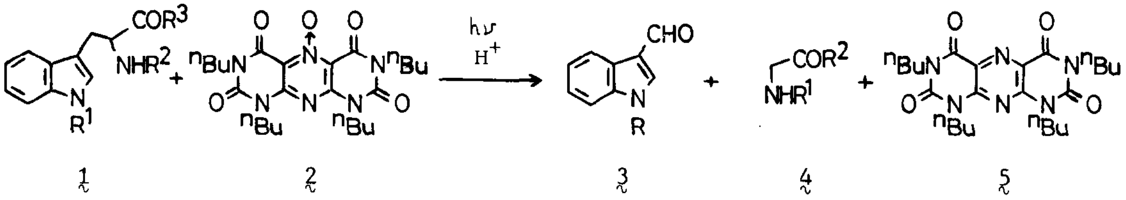
Abstract : Tryptophan derivatives **1** undergo with ease the oxidative C_α-C_β bond cleavage by pyrimido[5,4-g]pteridine N-oxide **2** under irradiation with UV-visible light in the presence of acid-catalyst to give 3-indolecarboxaldehydes **3** and the corresponding glycine derivatives **4**.

Herein we report a new type of photochemical oxidation of tryptophan derivatives **1**[1] by pyrimido[5,4-g]pteridine N-oxide **2**[2] resulting in the regioselective cleavage of the tryptophan side-chain[3] to give 3-indolecarboxaldehydes **3** and the corresponding glycine derivatives **4**, which has interesting mechanistic implication. The product, 3-indolecarboxaldehyde **3a**, has been observed in human adrenal tumour tissue as well as in normal pancreas and spleens[4] and as one of the metabolites of tryptophan in rats,[5] cabbage plants,[6] tomato plants,[7] holoparasitic dicotyledonus plants,[8] Ceratocystis fagacearum,[9] Endomycopsis vernalis,[10] and Cordyceps militaris.[11] Thus, the present result is also intriguing in connection with the metabolism of tryptophan in animals, plants, and microorganisms.[12]

When a mixture of L-tryptophan methyl ester **1a** [2.5 mM] and **2** [5.0 mM] in dry acetonitrile containing a catalytic amount of hydrogen chloride was irradiated with UV-visible light at ambient temperature under argon for 6 h, **3a** was isolated in 72% yield, together with glycine methyl ester **4a** and pyrimido[5,4-g]-pteridine **5**.[13] A certain amount of the starting materials **1a** and **2** were recovered. The other oxidized products of **1a** were not isolated under the conditions employed. The structures of the products **3a**, **4a**, and **5** were confirmed by the spectral comparison with these authentic samples.



1
a) R^1=H, R^2=H, R^3=OMe
b) R^1=H, R^2=H, R^3=OH
c) R^1=H, R^2=Ac, R^3=OEt
d) R^1=Me, R^2=H, R^3=OH
e) R^1=H, R^2=H, R^3=L-Tyr·OEt
f) R^1=H, R^2=L-Phe, R^3=OMe

3
a) R=H
b) R=Me

4
a) R^1=H, R^2=OMe
b) R^1=H, R^2=OH
c) R^1=Ac, R^2=OEt
d) R^1=H, R^2=L-Tyr·OEt
e) R^1=L-Phe, R^2=OMe

Scheme 1

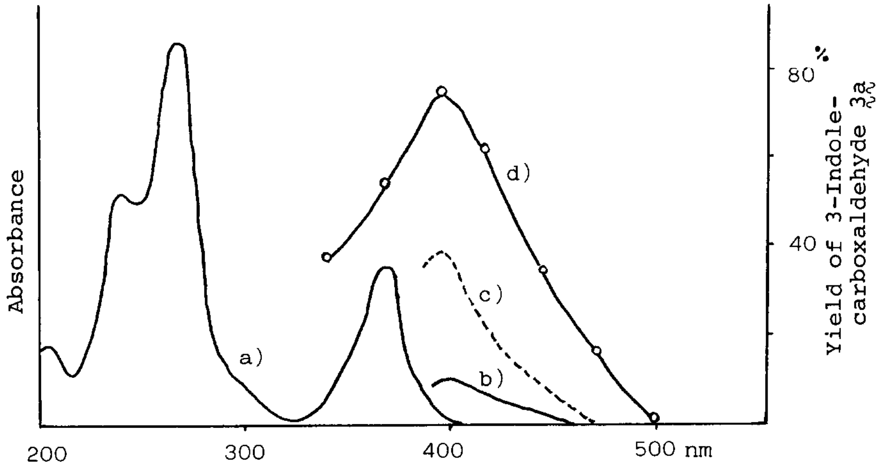


Figure 1. a) UV-visible absorption spectrum of pyrimido[5,4-*g*]pteridine *N*-oxide **2** [5x10^{-5}M] in MeCN. b) Difference spectrum of the mixture of **2** [3 mM] and L-tryptophan methyl ester **1a** [20 mM] vs. **2** [3 mM] in MeCN. c) Difference spectrum of the mixture of **2** [3 mM] and **1a** [20 mM] vs. **2** [3 mM] in MeCN in the presence of HCl [2 mM]. d) Wavelength dependence (presented by the yield of **3a**) in the photochemical C_α-C_β bond cleavage of **1a** by **2**. A solution of **1a**·HCl [2.5 mM]and **2** [5.0 mM] in MeCN was irradiated by using a grating monochromator (JASCO Model CRM-FA) with 2 KW Xe lamp and 4 nm band width under argon for 36 h.

When the reaction was carried out with shielding from light (e.g., reflux for 1 d), the products **3a**, **4a**, and **5** were not obtained and the starting materials **1a** and **2** were recovered unchanged. The photo-reaction of **1a** with **2** in the absence of hydrogen chloride afforded only small amounts of these products. Above facts clearly indicate that the irradiation in the presence of the acid-catalyst is requisite for the completion of the present reaction. The Charge-transfer (CT) interaction between **1a** and **2** in a ground-state was observed as evidenced by UV-visible absorption spectrum (see curve b in Figure 1). The absorption of the CT-complex (393 nm) was markedly enhanced by the addition of a

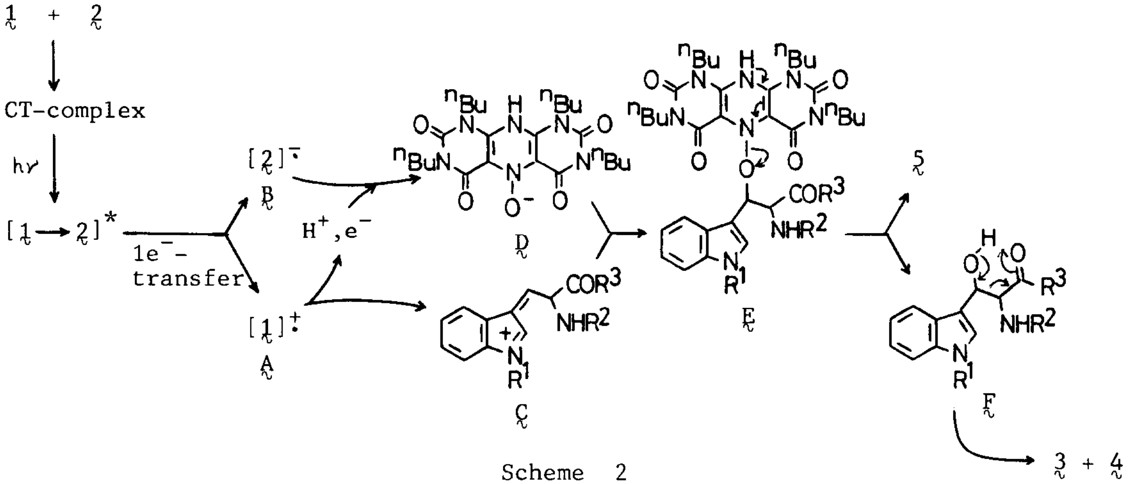
Table 1 Photochemical C_α-C_β Bond Cleavage of Tryptophan Side-Chain by Pyrimido[5,4-*g*]pteridine *N*-oxide **2**a)

Starting material b)	Irradiation time (h)	3-Indolecarboxaldehyde (**3**) Yield, % c)
L-tryptophan methyl ester (**1a**)	6	**3a** d) 72
L-tryptophan (**1b**)	10	**3a** 47
N-acetyl-L-tryptophan ethyl ester (**1c**)	4	**3a** 45
1-methyltryptophan (**1d**)	15	**3b** e) 38
L-tryptophanyl-L-tyrosine ethyl ester (**1e**)	4	**3a** 46
L-phenylalanyl-L-tryptophan methyl ester (**1f**)	6	**3a** 56

a)Irradiation was carried out by using Riko Rotary Photochemical Reactor Model RH-400-10W (400W high-pressure mercury arc lamp, external irradiation) through pyrex filter under argon. In the cases of **1b-f**, aqueous MeCN containing a catalytic amount of hydrogen chloride was employed as a solvent. The formation of the products **4b-e** and **5** was shown by TLC analysis and Mass spectrometry. b) Compounds **1a-d** are from Aldrich Chemical Co. or Sigma Chemical Co.. Compounds **1e** and **1f** were prepared by using the DCC-method. cf. J.C. Sheehan and G.P. Hess, J. Am. Chem. Soc., 1955, 77, 1067. c) Isolated yield. d) P.N. James and H.R. Snyder, Org. Syn., 1959, 39, 30. e) E. Wenkert, J.H. Udelhofen, and N.K. Bhattacharyya, J. Am. Chem. Soc., 1959, 81, 3763.

small amount of hydrogen chloride into the medium. (curve c) A strong wavelength dependence was observed in this photo-reaction: irradiation with a 393 nm light (CT-band) resulted in a maximum yield of the product **3a** as shown in Figure 1 (see curve d). The oxidative cleavage of the tryptophan side-chain was also observed in the reaction of a variety of tryptophan derivatives **1b-f**, including N_1- or terminal NH_2-protected tryptophanyl derivatives and tryptophanyl dipeptides, with **2**. (see Table 1)

Taking the above results and the capacity of indoles as an electron donor[14] into consideration, we present a plausible mechanism for the photolysis of **1** in the presence of **2** leading to **3**, **4**, and **5** as depicted in Scheme 2.



Scheme 2

The reaction can be initiated by the formation of the **1**/**2** CT-complex in a ground-state followed by a single-electron transfer (SET) from **1** to **2** in the exciplex to give the tryptophanyl cation radical **A** and _N_-oxide anion radical **B**. Subsequent proton- and electron-transfers from **A** to **B** give rise to an indolenium ion **C** and a nitroxyl anion **D**. Coupling of the resulting intermediate **C** with **D** leads to a transient adduct **E** and heterolytic fragmentation of the N-O bond in **E** gives **5** and the β-hydroxytryptophans **F**.[15,16] Elimination of the glycine moiety **4** from **F** proceeds under the conditions employed to give **3** ultimately. The remarkable effect of the acid-catalyst in the present reaction can be reasonably explained by considering the increased CT-complex formation in the initial step of the reaction. In agreement with the proposed SET mechanism, the formation of **3a** in the reaction of **1a** with **2** was markedly suppressed by the addition of tetracyanoethylene, a strong electron acceptor, into the reaction medium.

REFERENCES AND NOTES

1 Nakagawa et al have shown that irradiation of tryptamine derivatives with UV-light in the presence of pyridine _N_-oxide gives 2-oxindole derivatives and 3a-hydroxy-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-_b_]indole derivatives. cf. M. Nakagawa, T. Kaneko, H. Yamaguchi, T. Kawashima, and T. Hino, _Tetrahedron_, 1974,

30, 2591.

2 We have recently demonstrated that the *N*-oxide **2** transfers efficiently its oxygen to the substrate without any side-reactions under irradiation using UV-visible light: e.g., **2** oxidizes benzene, toluene, and anisole under irradiation using UV-visible light to give the corresponding phenol derivatives in a high yield, respectively, and *N,N*-dimethylaniline undergoes with ease the photochemical oxidative demethylation by **2**. These findings indicate that the photo-oxidation by **2** can be regarded as a formal chemical model of the monooxygenase. cf. M. Sako, K. Shimada, K. Hirota, and Y. Maki, *Tetrahedron Lett*., 1985, **26**, 6493 ; *idem*., *J. Am. Chem. Soc*., 1985, submitted.

3 Recently, Moriarty et al have reported an example of the oxidative cleavage of the tryptophan side-chain using $C_6H_5I(OAc)_2$/KOH/MeOH system to give 3-methoxymethylindole. However, the reaction was completely inhibited by the protection of the N_1-position and the terminal NH_2 group in tryptophan and the corresponding glycine derivatives **4** were not obtained in the reaction. cf. R.M. Moriarty and M. Sultana, *J. Am. Chem. Soc*., 1985, **107**, 4559.

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12 The photochemical oxidation with the *N*-oxide **2** was specific for tryptophan derivatives among the naturally occurring amino acids. Thus, the present reaction may be applicable to the modification of tryptophan residue in proteins.

13 A small amount of the degradation products of **3a** was detected by TLC analysis of the reaction mixture. The independent experiment showed that the product **3a** degradated gradually under the photochemical conditions in the presence of hydrogen chloride.

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15 β-Hydroxytryptophan derivative has been observed as a key intermediate in the oxidation of *N*-acetyl-L-tryptophanamide by Tryptophan side-chain oxidase leading to *N*-acetyl-α,β-didehydrotryptophanamide. cf. Y. Noda, K. Takai, T. Tokuyama, S. Narumiya, H. Ushiro, and O. Hayaishi, *J. Biol. Chem*., 1978, **253**, 4819; S. Ito, K. Takai, T. Tokuyama, and O. Hayaishi, *J. Biol. Chem*., 1981, **256**, 7834.

16 In the case of the reaction using aqueous MeCN as a solvent, an alternative process via the 1,4-addition of H_2O to **C** might be involved for the formation of **F**. cf. Ref. 3 and 15.

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