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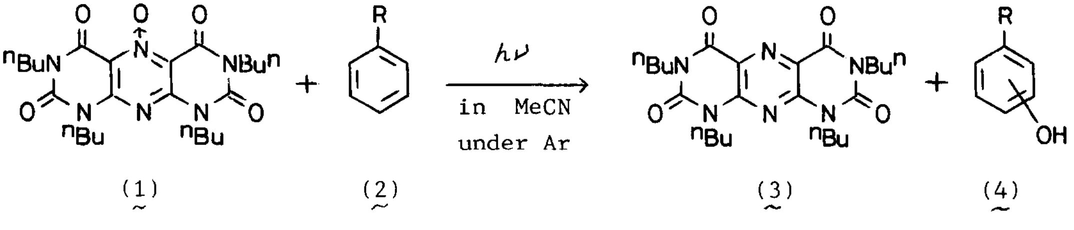
EFFICIENT OXYGEN-ATOM TRANSFER AGENT: PHOTOCHEMICAL HYDROXYLATION OF BENZENE DERIVATIVES BY PYRIMIDO[5,4-g]PTERIDINE N-OXIDE

Magoichi Sako, Kaoru Shimada, Kosaku Hirota, and Yoshifumi Maki,*
Gifu Pharmaceutical University, 6-1, Mitahora-higashi 5 Chome,
Gifu 502, Japan

Abstract: Pyrimido[5,4-g]pteridine N-oxide (1) oxidizes efficiently benzene, *toluene, and anisole under UV irradiation to give the corresponding phenol* derivatives 4, though the easiness of the reaction significantly depends upon the nature of the substituents on the benzene ring.

Photochemical hydroxylation of benzene derivatives by heterocycle N-oxides has been extensively investigated from viewpoint of bioorganic chemistry as one of the model systems for the biological oxidation of aromatic hydrocarbons which is catalyzed by hepatic monooxygenase, e.g., cytochrome P-450.[1] The complicated photochemical reactivities of the N-oxides so far employed in these investigations, however, has made it difficult to transfer efficiently an oxygen-atom from the N-oxides to the substrate.[2]

We now describe here that pyrimido[5,4-g]pteridine N-oxide (1), prepared with ease from 6-amino-5-nitrosouracil derivative,[3] is stable in acetonitrile under UV irradiation but oxidizes photochemically various benzene derivatives 2



R= H, Me, OMe

Scheme 1

without accompanying any side-reactions to give the corresponding phenol derivatives **4**. The present result indicates that the N-oxide **1** is an efficient oxygen-atom transfer agent and serves as a tool in the elucidation of the mechanism, remaining equivocal as yet, on the photochemical oxygen-atom transfer reaction by the heterocycle N-oxides.[2]

A solution of **1** (0.5 mmol) and a large excess amount of benzene (100 mmol) in acetonitrile (200 ml) was irradiated by using a 400W high pressure mercury arc lamp through pyrex filter under argon atmosphere for 2 h. GC analysis of the reaction mixture showed the formation of phenol (42% yield based on **1** employed) and column chromatography of the residue obtained after evaporation of the solvent allowed isolation of the deoxygenated product **3** in 45% yield together with the recovered N-oxide **1**.[4] TLC and GC analyses of the reaction mixture showed that there was no detectable amount of other products in this reaction. The structure of **3** was confirmed by direct comparison with an authentic sample prepared by the reduction of **1** with sodium hydrosulfite.[5] The product **3** is stable under the reaction conditions. Analogous results were also obtained by employment of toluene and anisole in place of benzene as summarized in Table 1. In these reactions, no formation of the products resulting from the oxidation of the side-chain on the benzene ring was shown by GC analysis.[6]

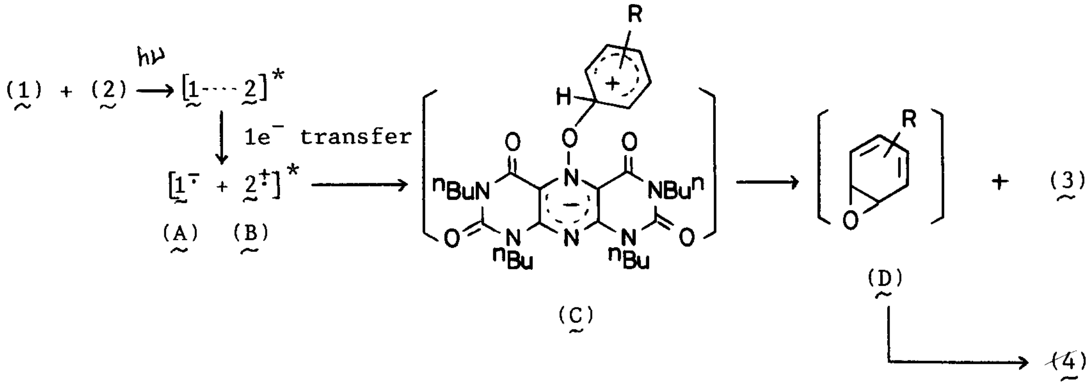
Table 1 Photochemical Reaction of Pyrimido[5,4-g]pteridine N-oxide (**1**) with Benzene Derivatives **2**

2 R	Yield of **4** a) (%)	Consumption Rates of **1** d) 10^6 k' s^{-1}
H	42	1.92
Me	64 b)	3.99
OMe	50 c)	12.50
		0.08 e)

a) Based on **1** employed. A significant amount of **1** was recovered in every cases since a prolonged reaction time in these reactions caused decrease in the yield of the oxidation products. b) Reaction condition: **1** [2.5 mmol], toluene [500 mmol], in MeCN, for 2 h. Product distribution: o-isomer / p- and/or m-isomers = 7 / 9. c) Reaction condition: **1** [2.5 mmol], anisole [25 mmol], in MeCN, for 3 h. Product distribution: o-isomer / p-isomer = 1 / 10. d) Condition: A solution of **1** [1.0 mmol] in MeCN was irradiated under argon atmosphere in the absence or presence of **2** [10.0 mol]. e) In the absence of **2**.

In contrast to the above results, cyanobenzene and ethyl benzoate were not oxidized by **1** even after a prolonged reaction time. The consumption rates of **1** in acetonitrile under UV irradiation were remarkably affected by the presence of **2** as shown in Table 1. The Table clearly shows that the conversion rate of **1** and the easiness of the photochemical oxidation of **2** by **1** significantly depend upon the nature of the substituents on the benzene ring, suggesting that there would be an interaction between **1** and **2** in this photo-reaction.

Taking these facts and the capacity of **1** as an electron acceptor[7] into considerations, we present a conceivable reaction sequence for the present reaction as depicted in Scheme 2.



Scheme 2

The reaction could be initiated by the formation of a exciplex between the N-oxide **1** and the benzene derivatives **2**. The donation of an electron from **2** to **1** in the exciplex gives a N-oxide radical anion (**A**) and a radical cation (**B**). The resulting radical anion **A** could be combined with **B** in a cage to form a coupling product (**C**). The fission of the N-O bond in **C** results in the formation of a dihydroarene oxide intermediate (**D**),[8] which could be easily converted into the final product **4**, and the deoxygenated product **3**.

This finding is suggestive of the presence of an alternative process in the photochemical hydroxylation of the aromatic hydrocarbons by the heterocycle N-oxides.[2]

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d) T. Tsuchiya, H. Arai, and H. Igeta, *ibid.*, **1970**, 2213; e) W. H. Rastetter, T. R. Gadek, J. P. Tane, and J. W. Frost, *J. Am. Chem. Soc.*, **1979**, *101*, 2228; f) M. N. Akhtar, D. R. Boyd, J. D. Neill, and D. M. Jerina, *J. Chem. Soc., Perkin I*, **1980**, 1693; g) Y. Ogawa, S. Iwasaki, and S. Okuda, *Tetrahedron Lett.*, **1981**, *22*, 2277 and 3637.

2. For recent reviews concerning photochemistry of the heterocycle *N*-oxides, see: G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **1970**, *70*, 231; A. Albini and M. Alpegiani, *ibid*, **1984**, *84*, 43. It has been proposed that the photochemical oxygen-atom transfer reaction by the *N*-oxides is induced by the active oxygen species such as oxene or oxazilidine intermediate arising from the excited *N*-oxides.

3. Y. Maki, M. Sako, and E. C. Taylor, *Tetrahedron Lett.*, **1971**, 4271; E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, **1972**, *37*, 1601. UV spectrum of **1** in MeCN: 370(2.2×10^4), 270(5.0×10^4), 242(3.2×10^4)nm.

4 Photochemical oxidation of benzene by the heterocycle *N*-oxides is one of the one-step synthesis of phenol. From this reason, a few attempts have been made to enhance the formation of phenol in this reaction. The present method is advantageous as the synthetic method of phenol compared with those methods. cf. G. Serra-Errante and P. G. Sammes, *J. Chem. Soc., Chem. Commun.*, **1975**, 573; N. Hata, I. Ono, and M. Kawasaki, *Chem. Lett.*, **1975**, 25; P. G. Sammes, G. Serra-Errante, and A. C. Tinker, *J. Chem. Soc., Perkin I*, **1978**, 853; S. Ito and K. Sasaki, *J. Syn. Org. Chem. Japan*, **1983**, *41*, 839.

5 mp 113-116°C (from EtOH-H_2O); ^1H NMR($CDCl_3$) δ: 0.75-1.15(12H,m), 1.20-2.00 (8H,m), 3.75-4.50(8H,m); IR(KBr): 1730 and 1680(C=O) cm^{-1}; UV(MeCN): 371 (1.7×10^4), 364(1.9×10^4), 357(1.7×10^4), 272(8.3×10^3), 236(3.1×10^4)nm; MS *m/e*: 472(M^+), 430, 417.

6 These reactions did not proceed in the dark (reflux for 10 h), clearly indicating that UV irradiation is requisite for the completion of the reaction.

7 When *N*,*N*-dimethylaniline (DMA) was added to a solution of **1** in acetonitrile, the absorption of CT-complex formed between **1** and DMA was observed in the position (412 nm) apparently different from that of **1**.

8 It has been already demonstrated that dihydroarene oxides are transient intermediates initially formed in both enzymatic and non-enzymatic (by heterocycle *N*-oxides) oxidations of the aromatic hydrocarbons. cf. J. W. Daly, D. M. Jerina, and B. Witkop, *Experientia*, **1972**, *28*, 1129; D. M. Jerina, H. Yagi, and J. W. Daly, *Heterocycles*, **1973**, *1*, 267; ref. 1f; B. J. Auret, S. K. Balani, D. R. Boyd, R. M. E. Greene, and G. A. Berchtold, *J. Chem. Soc., Perkin Trans I*, **1984**, 2659; D. R. Boyd and D. M. Jerina, in 'The Chemistry of Heterocyclic Compounds. Small Ring Heterocycles', Part III, ed. A. Hassner, Wiley, New York, **1984**, *24*, p197; K. Korzekwa, W. Trager, M. Gouterman, D. Spangler, and G. H. Loew, *J. Am. Chem. Soc.*, **1985**, *107*, 4273; E. D. Bush, W. F. Trager, *J. Med. Chem.*, **1985**, *28*, 992.

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