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# PHOTO-OXIDATIVE CYCLISATION OF 2'-HYDROXYCHALCONES LEADING TO FLAVONES INDUCED BY HETEROCYCLE N-OXIDES : HIGH EFFICIENCY OF PYRIMIDO[5,4-g]PTERIDINE N-OXIDE FOR THE PHOTOCHEMICAL DEHYDROGENATION [†]

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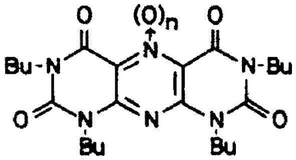
**Abstract** : Irradiation of 2'-hydroxychalcones (3) with UV-visible light in the presence of heterocycle N-oxides such as pyrimido[5,4-g]pteridine N-oxide (1) results in the formation of the corresponding flavones (4) and flavanones (5). The photo-oxidative cyclisation of (3) induced by (1) to give (4) most efficiently occurred among the heterocycle N-oxides examined and could be reasonably explained by considering an initial single-electron oxidation of (3) by (1) under the photochemical conditions and subsequent intramolecular cyclisation.

## INTRODUCTION

Photochemistry of heterocycle N-oxides is formally classified into two reaction modes which consist of the photo-rearrangement and the photochemical oxygen-atom transfer reaction. [1] The latter reaction is of interest as one of the functional chemical models for the biological oxidations catalised by hepatic monooxygenases, e.g., cytochrome P-450. [2] The complicated photochemical reactivities of the N-oxides so far employed, however, have made it difficult to transfer efficiently the oxygen-atom of the N-oxides to the substrates and consequently to clarify the mechanism for the oxygen-atom transfer reaction.

In the course of our search for the heterocycle N-oxides having the high capacity for the oxygen-atom transfer rather than the photo-rearrangement, our attention has been focused to the pyrimido[5,4-g]pteridin-2,4,6,8(1H,3H,7H,9H)-tetrone 5-oxide system (cf. 1) which is readily available [3] and has the N-oxide function uniquely positioned between two neighboring carbonyl groups and on the electron-deficient pyrazine ring annelated with two uracil rings.



(1) : n = 1
(2) : n = 0

Scheme 1

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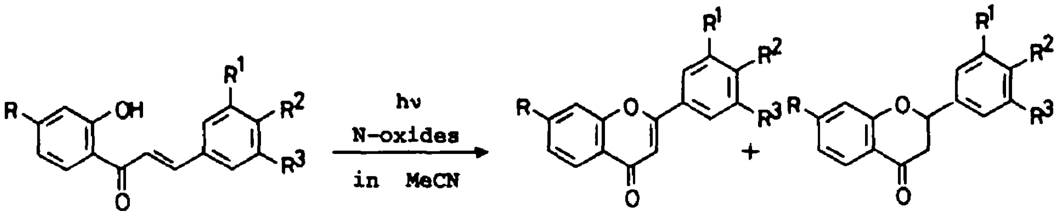
[†] This contribution is dedicated to Professor Edward C. Taylor on the occasion of his 65th birthday.

In agreement with our anticipation, pyrimido[5,4-g]pteridine N-oxide (1) transfered smoothly its oxygen-atom to various substrates without unfavorable side-reactions under the photochemical conditions, e.g., a) the N-oxide (1) oxidised benzene, toluene, and anisole under irradiation with UV-visible light to give the corresponding phenol derivatives in comparatively high yields; [4a] b) N,N-dimethylaniline underwent with ease the oxidative demethylation by (1) under irradiation; [4b] c) the photochemical oxidative $C_\alpha$-$C_\beta$ bond-cleavage of the tryptophan side-chain was induced by (1) to give 3-formylindole and glycine derivatives. [4c] These reactions can be accounted for by the reaction sequences involving an initial single-electron-transfer ( SET ) from the substrates to (1) and subsequent oxygen-atom transfer, which is suggestive of the presence of an alternative process, not involving the active oxygen species such as oxene or oxazilidine intermediates arising from the excited N-oxides as previously proposed,[1] in the photochemical oxidation by the heterocycle N-oxides. It is noticeable that these reaction sequences formally parallel the mechanism proposed for the biological oxidations catalised by cytochrome P-450. [5]

On the other hand, we have demonstrated that 2',3'-O-isopropylidenepurine nucleosides undergo an intramolecular oxidative cyclisation under irradiation in the presence of (1) to give the corresponding 5'-O,8-cyclopurine nucleosides [4d] and the introduction of benzoyl groups at the $N^6$-position of 5'-protected adenosines causes the oxidative photo-cyclisation by (1) leading to quinazolinopurine nucleosides. [4e] These facts show that (1) also acts as an oxidant for the dehydrogenation of the substrates under the photochemical conditions resulting in the formation of pyrimido[5,4-g]pteridine (2) and water without the oxygen uptake by the substrates. The role of (1) in these reactions is functionally similar to that of dehydrogenases *in vivo*.

This paper describes a novel photochemical dehydrogenation of 2'-hydroxychalcones (3) induced by the heterocycle N-oxides to give the corresponding flavones (4) which proceeds *via* an initial SET process. The reaction occurred most effectively in the case of the N-oxide (1) among the heterocycle N-oxides examined and competed with the photochemical isomerisation of (3) leading to flavanones (5). The present result is also of interest in connection with the biosynthesis of flavones.



(3) (4) (5)

| | R | R1 | R2 | R3 |
|---|---|---|---|---|
| a | H | H | H | H |
| b | H | H | Me | H |
| c | H | H | OMe | H |
| d | H | OMe | OMe | H |
| e | H | OMe | OMe | OMe |
| f | H | H | Cl | H |
| g | H | H | Br | H |
| h | OMe | H | H | H |

Scheme 2

## RESULTS AND DISCUSSION

A mixture of 2'-hydroxychalcone (**3a**) and the *N*-oxide (1) in dry acetonitrile was irradiated with UV-visible light under argon until disappearance of (1) was completed After removal of the solvent, the residue was chromatographed to give flavone (**4a**) and flavanone (**5a**) in 62% and 20% yields, respectively, together with the deoxygenated product (2). TLC analysis of the reaction mixture showed the absence of a detectable amount of other products in this reaction. Analogously, irradiation of other 2'-hydroxychalcone derivatives (**3b–h**) in the presence of (1) gave the corresponding flavones (**4b–h**) and flavanones (**5b–h**). The photo-oxidative cyclisation of (**3a**) leading to (**4a**) was also observed by employment of other heterocycle *N*-oxides such as pyridine *N*-oxide, quinoline *N*-oxide, 4-nitropyridine *N*-oxide, 3,10-dibutylisoalloxazine 5-oxide, [4b] and phenazine *N*-oxide in place of (1). Their efficiency as an oxidant, however, is lower than that of (1). All results of the photochemical reactions of (3) induced by the heterocycle *N*-oxides are summarised in Table 1. The formation of (4) was not observed in the absence of these *N*-oxides or in the dark (e.g., reflux for 12 hr).

**Table 1 Photochemical Reactions of 2'-Hydroxychalcones (3) Induced by Heterocycle *N*-Oxides [a]**

| Entry No. | Chalcones | *N*-Oxides | React. Time (min) | Products [b] (4) (%) [c] | Mp (°C)(lit.) | (5) (%) [c] | Mp (°C)(lit.) |
|---|---|---|---|---|---|---|---|
| 1 | (3a) | (1) | 50 | (4a)(62) | 96-7 (97 [d]) | (5a)(20) | 75 (75-6 [e]) |
| 2 | (3b) | (1) | 45 | (4b)(63) | 115-6 (116 [f]) | (5b)(19) | 71-2 (73 [g]) |
| 3 | (3c) | (1) | 33 | (4c)(72) | 156-8 (157-8 [h]) | (5c)( 6) | 94-6 (97 [i]) |
| 4 | (3d) | (1) | 22 | (4d)(66) | 155 (154-5 [j]) | (5d)( 4) | 125 (123-5 [j]) |
| 5 | (3e) | (1) | 20 | (4e)(68) | 174-5 (174 [k]) | (5e)( 4) | 131-3 (132-3 [l]) |
| 6 | (3f) | (1) | 47 | (4f)(55) | 189 (188-9 [m]) | (5f)(28) | 88-9 (87 [n]) |
| 7 | (3g) | (1) | 52 | (4g)(53) | 177-8 (178 [o]) | (5g)(30) | 115-6 (117 [o]) |
| 8 | (3h) | (1) | 45 | (4h)(60) | 110 (111 [p]) | (5h)(13) | 91 (91 [q]) |
| 9 | (3a) | PO | 240 | (4a)( 8) | | (5a)(26) | |
| 10 | (3a) | QO | 140 | (4a)( 1) | | (5a)(24) | |
| 11 | (3a) | 4-NPO | 70 | (4a)(46) | | (5a)(14) | |
| 12 | (3a) | IAO | 65 | (4a)(24) | | (5a)(13) | |
| 13 | (3a) | PZO | 20 | (4a)(13) | | (5a)(10) | |

a) In all reactions, the corresponding deoxygenated products of the employed *N*-oxides were obtained. b) All known products gave spectral data in agreement with their structures. c) Isolated yield based on (3) consumed. d) S. von Kostanecki and J. Tambor, Chem. Ber., **28**, 2032 (1895). e) S. von Kostanecki and W. Szabranski, Chem. Ber., **37**, 2634 (1904). f) F. D. Cramer and G. H. Elschnig, Chem. Ber., **89**, 1 (1956). g) K. -K. Hsu and J. -Y. Shi, J. Chin. Chem. Soc., **20**, 51 (1973). h) K. von Auwers and L. Anshutz, Chem. Ber., **54**, 1543 (1921). i) A. Edelstein and S. von Kostanecki, Chem. Ber., **38**, 1507 (1905). j) J. Berstein, C. Frashina, and S. von Kostanecki, Chem. Ber., **38**, 2177 (1905). k) S. Hattori, Acta Phytochem., **6**, 131 (1932). l) Z. Witczak and M. Krolikowska, Pol. J. Chem., **53**(5), 1033 (1979). m) W. Baker, J. B. Harborne, and W. D. Ollis, J. Chem. Soc., 1294 (1952). n) P. L. Cheng, P. Fournari, and J. Tirouflet, Bull. Soc. Chim. France, 2248, (1963). o) T.-C. Chen and C.-H. Yang, J. Taiwan Pharm. Assoc., 3, 39 (1951). p) T. Emilewicz and S. von Kostanecki, Chem. Ber., **32**, 309 (1899). q) S. von Kostanecki and M. L. Stoppani, Chem. Ber., **37**, 1180 (1904). (Abbreviation : PO = pyridine *N*-oxide; QO = quinoline *N*-oxide; 4-NPO = 4-nitropyridine *N*-oxide; IAO = 3,10-dibutylisoalloxazine 5-oxide; PZO = phenazine *N*-oxide)

The flavanones (5) was obtained together with (4) in every cases of the photochemical reaction of (3) with (1) as shown in Table 1 and (3) photochemically isomerised to (5) under the conditions employed. [6] Thus, it can be considered that (5) is an intermediate for the formation of (4) in this reaction. Irradiation of a mixture of (**5a**) and (1) under the analogous conditions, however, gave (**4a**) only in 7 % yield along with the isomerised product (**3a**)(18% yield), resulting in recovery of a large quantity of the starting materials (1) and (**5a**). This fact clearly indicates that (5), formed by the photochemical isomerisation of (3), is not a productive intermediate for the formation of (4).

The difference spectrum ( $\lambda_{max}$ : 404 nm) of a mixture of (**3a**)($\lambda_{max}$ : 351, 317, and 221 nm) and (1)($\lambda_{max}$ : 370, 270, and 242 nm) vs. (1) in dry acetonitrile showed the presence of a weak charge-transfer interaction between (1) and (**3a**) in the ground-state. Excitation of the charge-transfer complex with a 404 nm light is much more inefficient for the formation of (**4a**) than that of (1) and (**3a**) with 350-370nm lights. Thus, the present photoreaction appears to be initiated by excitation of either (1) or (3).

Fig. 1 illustrates the plot of the consumption-rate constants (-log k) of the N-oxide (1) vs. the cathodic peak potentials ($E^{ox}_{p}$) of the 2'-hydroxychalcones (3) indicating an excellent linear relationship (r= 0.997, $\rho$= 0.705). This relationship with the positive $\rho$ value is suggestive of the involvement of SET process in the present photoreaction.

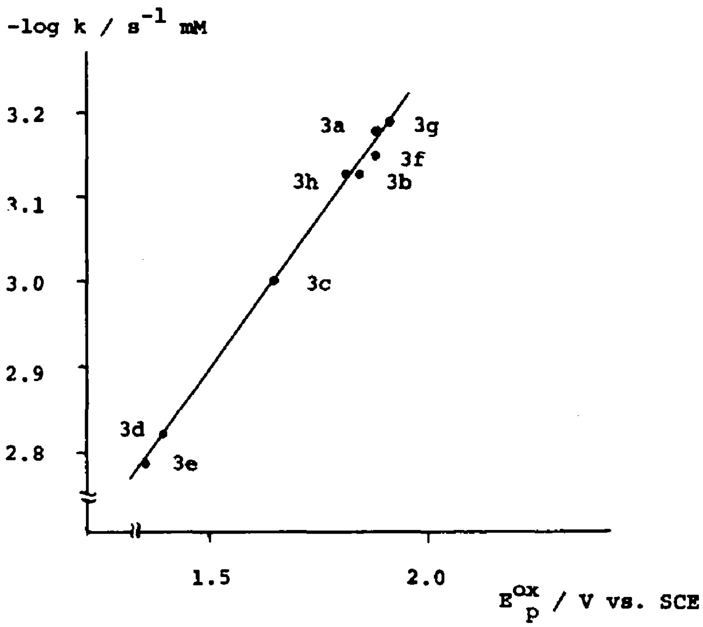
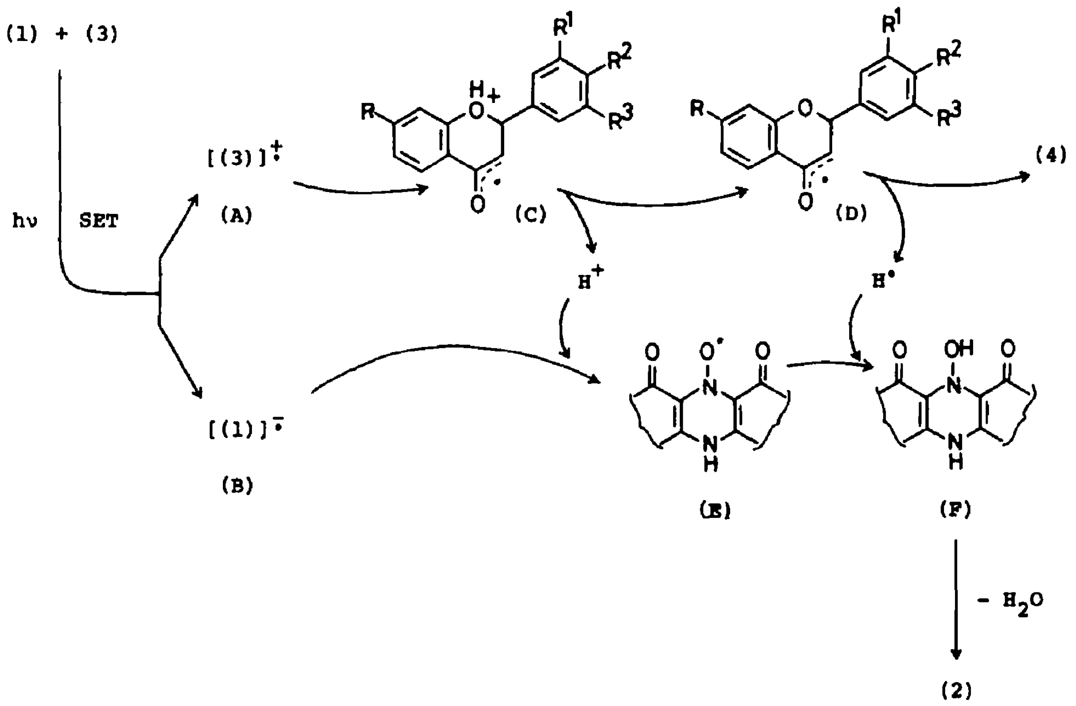


Fig. 1 Correlation between the cathodic peak potentials ($E^{ox}_{p}$) of the 2'-hydroxychalcones (**3a-h**) and measured consumption-rate constants (-log k) of pyrimido[5,4-g]pteridine N-oxide (1) in the photochemical reaction of (**3a-h**) with (1). The cathodic peak potentials of (**3a-h**) were measured by cyclic voltammetry under the following conditions : [(**3a-h**)] = $3\times10^{-3}$ mol dm$^{-3}$, [n-$Bu_4NClO_4$] = 0.1 mol dm$^{-3}$, scan rate = 0.2 V s$^{-1}$, in acetonitrile, at 18°C.

Taking into consideration the above facts, a possible reaction sequence for the present oxidative cyclisation of (3) leading to (4) photochemically induced by (1) is depicted as shown in Scheme 3. In the initial stage of the photoreaction, the facile SET from (3) to (1) occurs by excitation of either (1) or (3) under the photochemical conditions, resulting in the generation of a chalcone cation radical (**A**) and an *N*-oxide anion radical (**B**). The cation radical (**A**) undergoes the intramolecular cyclisation to give an intermediate (**C**). The radical anion (**B**) could capture a proton from (**C**) to produce radicals (**D**) and (**E**). Hydrogen abstraction from (**D**) by (**E**) and subsequent dehydration of the resulting transient intermediate (**F**) could give ultimately the flavones (4) and the pyrimido[5,4-*g*]pteridine (2). In agreement with the involvement of the SET process, the present oxidative cyclisation of (3) to give (4) was also accomplished by the employment of tetracyanoethylene (TCNE) or tetracyanoquinodimethane (TCNQ), a well-known electron acceptor, in the place of (1).[7]



**Scheme 3**

The effect of UV-irradiation on the biosynthesis of flavonoids has been widely investigated[8] and consequently it has been considered that the 2'-hydroxychalcones is an important precursor in the biosynthesis of the flavonoids.[9] Along this line, the photochemical reactions of the 2'-hydroxychalcones involving the cis-trans photoisomerisation[10] and the ring-closure to flavanones[6a] have been reported. The photochemical oxidation of the 2'-hydroxychalcones, however, is unprecedented except its photo-oxygenation by singlet oxygen.[11] The present photoreaction is the first example of photo-induced oxidative cyclisation of the 2'-hydroxychalcones to give the flavones.

At present, the biosynthetic pathway of the flavones starting from the 2'-hydroxychalcones is not clear.[12] Pelter et al.[13] has suggested that a radical intermediate formed via single-electron oxidation of the 2'-hydroxychalcones would play an important role in the biosynthesis of the flavones. The present photocyclisation of (3) leading to (4) is regarded as a mimic for the biosynthetic pathway proposed by Pelter et al..

The high efficiency of (1) for the photochemical dehydrogenation as well as the photochemical oxygen-atom transfer will be discussed elsewhere on the basis of the physicochemical study on (1) and its structually related heterocycle N-oxides.

## EXPERIMENTAL

All melting-points were determined on a Yanagimoto melting-point hot-stage apparatus and are uncorrected. Irradiation was carried out under argon atmosphere by using a 400W high-pressure mercury arc lamp ( Riko Kagaku Sangyo ) through a Pyrex filter. Cathodic peak potentials were recorded on a Yanaco polalographic analyzer P-1100. Wakogel C-100 was used as silica gel for columun chromatography. Thin-layer chromatography (TLC) was run on silica gel 60 plates (Merck Art 5721). TLC-scan for measuring kinetics of the reaction was performed on a Hitachi 556 spectrophotometer with TLC-densitometer.

**2'-Hydroxychalcones (3a-h)** --- The chalcones (3a-h) were prepared with ease by the condensation of the corresponding benzaldehyde derivatives with 2-hydroxyacetophenones according to the known procedures.[14] All known products (3a-h) gave satisfactory spectral data consistent with their structures.

**Photochemical Reactions of (3a-h) with Pyrimido[5,4-g]pteridine N-Oxide (1): Typical Example** --- A mixture of (3a)(224 mg, 1.0 mM) and (1)(997 mg, 2.0 mM)[15] in dry acetonitrile (1000 ml) was irradiated at ambient temperature until disappearance of (1)(monitored by TLC) was completed (for 50 min). After removal of the solvent under reduced pressure, the residue was chromatographed by using benzene/ethyl acetate (30 : 1) as eluent to give flavone (4a)(138 mg, 62%) and flavanone (5a)(45 mg, 20%), together with a large amount of pyrimido[5,4-g]pteridine (2)(>90% based on (1) employed). ( See entry 1 in Table 1)

Analogously, the photochemical reactions of other 2'-hydroxychalcones (3b-h) with (1) were carried out under the conditions analogous to that of the case of (3a). The results of this reaction are summarised in Table 1. (See entry 2-8 in Table 1)

**Photochemical Reactions of (3a) with Pyridine N-Oxide, Quinoline N-Oxide, 4-Nitropyridine N-Oxide, 3,10-Dibutylisoalloxazine 5-oxide, or Phenazine N-Oxide** --- A mixture of (3a)[1.0 mM] and each N-oxide [2.0 mM] in dry acetonitrile was irradiated until the employed N-oxide disappeared and then worked up as mentioned above to give (4a) and (5a) together with the starting material (3a) unchanged. All results are summarised in Table 1. ( See entry 9-13 in Table 1)

**Photochemical Reactions of (3a) with TCNE or TCNQ** --- A mixture of (3a)[1.0 mM] and TCNE [2.0 mM] in dry acetonitrile was irradiated for 50 min under the conditions analogous to that of the reaction of (3a) with (1) and then worked up to give (4a) and (5a) in 17 and 36% yields, respectively. Analogously, irradiation of (3a) in the presence of TCNQ for 240 min gave (4a)(8%) and (5a)(61%).

**Photochemical Reactions of Flavanone (5a) in the Presence of (1)** --- A mixture of (5a)(224 mg, 1.0 mM) and (1)(977 mg, 2.0 mM) in dry acetonitrile (1000 ml) was irradiated for 50 min. After removal of the solvent under reduced pressure, the residue was chromatographed by eluting with a mixed solvent (benzene : ethyl acetate = 30 : 1) to give (3a)(40 mg, 18%) and (4a)(16 mg, 7%), together with (2)(890 mg, 94% yield based on (1) employed) and the unchanged starting material (5a)(150 mg, 67%).

**Measurement of Consumption Rate of (1) in the Photochemical Reactions of (3) with (1)** --- The consumption rate constants were followed spectrophotometically by measuring disappearance of (1) in the reaction with TLC-scanner. (Rf value of (1) = 0.15; eluent: benzene/ethyl acetate (5 : 1); wavelength of detector: 270nm) The values of k were calculated by plotting $A_t/A_0$ vs. time ($A_0$ = the initial peak area of (1), $A_t$= the peak area of (1) after irradiation for *t* min).

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15 The photochemical conversion of 2'-hydroxychalcones (**3**) into flavones (**4**) was also observed upon employment of an equimolar amount of pyrimido[5,4-g]pteridine N-oxide (**1**). In this case, the yield of (**4**) was reduced to some extent because of the consumption of (**1**) in other uncertain reactions. Therefore, excess (**1**)(2 moles) was employed for the preparative purpose.