Chem. Pharm. Bull. 39(1) 195—198 (1991)

A Novel Example of Thermal Oxygenation of Aromatic Hydrocarbons with a Heterocyclic *N*-Oxide: Unusual Reactivity of Pyrimido[5,4-*g*]pteridinetetrone 10-Oxide

Magoichi SAKO, Seiji OHARA, Kosaku HIROTA, and Yoshifumi MAKI*

Gifu Pharmaceutical University, 5–6–1, Mitahora-higashi, Gifu 502, Japan.

Received July 9, 1990

Aromatic hydrocarbons, *i.e.*, benzene, naphthalene (4), phenanthrene (6), toluene (10), *p*-xylene (14), mesitylene (18), and durene (21), were oxygenated by a member of a novel class of heterocyclic *N*-oxides, 1,3,6,8-tetrabutylpyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxide (1), under certain thermal conditions to give the corresponding products oxygenated in either the benzene ring or the methyl group, presumably *via* a single-electron transfer process.

Keywords thermal oxygenation; aromatic hydrocarbon; heterocyclic *N*-oxide; pyrimido[5,4-*g*]pteridinetetrone 10-oxide; single-electron transfer process

Previous articles from our laboratory[1] have demonstrated that under photochemical conditions, 1,3,6,8-tetrabutylpyrimido[5,4-*g*]pteridine-2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone 10-oxide (**1**) ($E_{1/2}^{red} = -0.97$ V *vs.* SCE in MeCN) functions as an electron acceptor and consequently as an agent for oxygenation or dehydrogenation, depending upon the nature of the substrates. For example, the photooxygenation of benzene, toluene, and anisole by **1** efficiently gives the corresponding phenols as major products without any photochemical intramolecular rearrangement of the *N*-oxide function. The reaction can be rationalized in terms of the involvement of an initial single-electron transfer (SET) from the benzenes to a singlet-excited **1** followed by oxygen-atom transfer, in contrast to the oxene mechanism which is generally accepted for photochemical oxygenation by heterocyclic *N*-oxides.[2]

Despite abundant examples of thermal deoxygenation of heterocyclic *N*-oxides by various reactants,[3] there is no precedent for the deoxygenation of heterocyclic *N*-oxides by aromatic hydrocarbons under thermal conditions, resulting in the oxygenation of the aromatic hydrocarbons employed.

In this paper, we wish to report that the unusual properties of the *N*-oxide **1** allow thermal oxygenation of aromatic hydrocarbons, *i.e.*, benzene, naphthalene (**4**), phenanthrene (**6**), toluene (**10**), *p*-xylene (**14**), mesitylene (**18**), and durene (**21**), presumably *via* a SET process followed by an oxygen-atom transfer process. To our knowledge, this is a first example of thermal oxygenation of aromatic hydrocarbons with a heterocyclic *N*-oxide.

When a mixture of benzene (2 M) ($E_{1/2}^{ox} = 2.68$ V *vs.* SCE)[4a] and **1** (5 mM) in dry acetonitrile was heated in a degassed tube at 135 °C in the dark for 1 d, the employed *N*-oxide **1** was recovered and no detectable amount of phenol was formed. Under similar conditions, the reaction of naphthalene (**4**) ($E_{1/2}^{ox} = 1.81$ V *vs.* SCE)[4a] with **1** gave naphthols (**5**) (as a mixture of 1- and 2-isomers in a ratio of 7 : 1) and 1,3,6,8-tetrabutylpyrimido[5,4-*g*]pteridine-

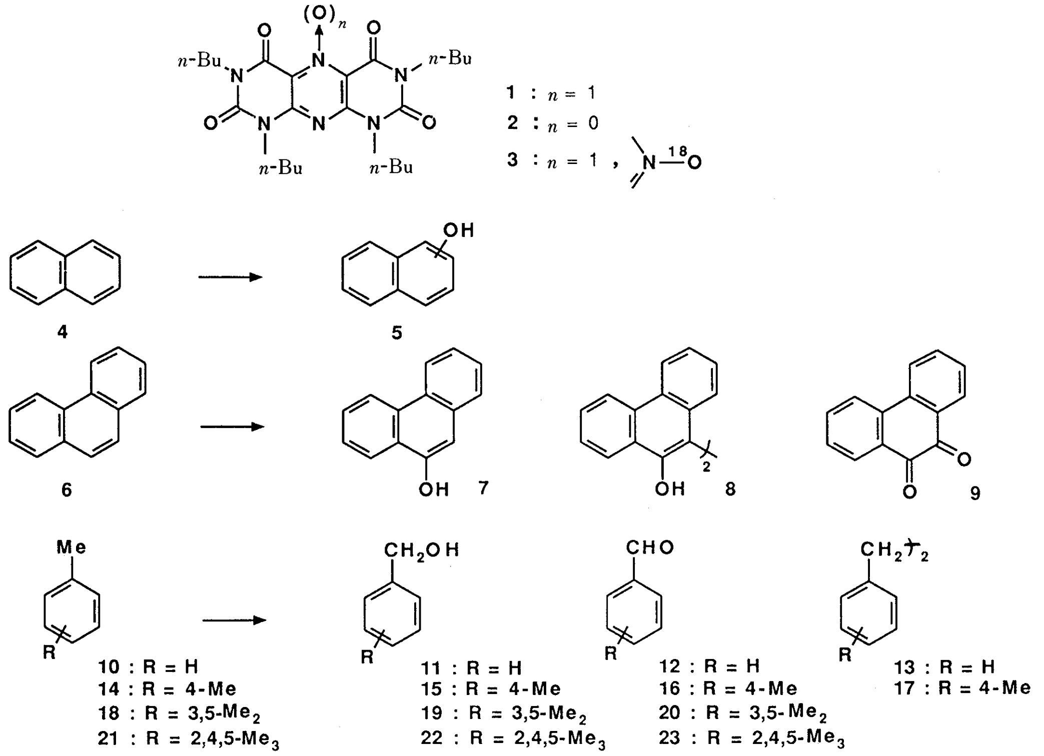

Chart 1

2,4,5,7(1*H*,3*H*,6*H*,8*H*)-tetrone (**2**) in 18 and 40% yields, respectively. Although a significant amount of **1** was recovered in this reaction, deoxygenation of **1** to **2** occurred without any other reaction. The reaction of **4** with ^{18}O-labeled *N*-oxide (**3**)[5] confirmed that the transfer of the *N*-oxide oxygen of **3** into **4** is virtually quantitative. The oxygenation of phenanthrene (**6**) ($E^{ox}_{1/2}=1.74$ V *vs.* SCE)[4a] by **1** under similar conditions resulted in the formation of 9-phenanthrol (**7**) (4%), bis(9-hydroxyphenanthren-10-yl) (**8**) (20%),[6] and 9,10-phenanthrenedione (**9**) (17%)[6] after complete consumption of **1**. When the thermal reaction of degassed benzene with **1** in a sealed tube at 135 °C was carried out without solvent, the formation of phenol in 5% yield was observed along with 13% consumption of **1**. Thus, it is evident that the thermal oxygenation of the aromatic hydrocarbons, benzene, **4**, and **6** by **1** occurs more easily as the oxidation potential decreases.

The charge-transfer (CT) interaction between **1** and **4** [405 ($\varepsilon=10$) nm] as well as between **1** and **6** [405 ($\varepsilon=16$) nm)] was evidenced by the difference ultraviolet (UV)-visible absorption spectrum of the mixture of **1** and **4** or **6** *vs.* **1**. The oxygenation of **4** and **6** by **1** was markedly accelerated by irradiation with UV-visible light, as previously demonstrated.[7]

These facts indicate that the oxygen-atom transfer from **1** to **4** or **6** probably occurs *via* SET from the substrates, **4**, and **6**, to **1** in the initially formed CT complexes.

Degassed toluene (**10**) ($E^{ox}_{1/2}=2.37$ V *vs.* SCE)[4b] was allowed to react with **1** in a sealed tube at 135°C in the dark. The *N*-oxide **1** was completely consumed after 1 d being converted into **2**. Benzyl alcohol (**11**) and benzaldehyde (**12**) were obtained in 68 and 18% yields, together with a trace amount of dibenzyl (**13**). It is noteworthy that no formation of any cresols was observed, which is in contrast to the case of the photochemical oxygenation of **10** by **1**, leading to *o*- and *p*-cresols as major products.[2] Employment of 3-methylpyridazine 2-oxide[8] in place of **1** resulted in no appreciable reaction under thermal conditions.

Under similar conditions, *p*-xylene (**14**) ($E^{ox}_{1/2}=2.06$ V *vs.* SCE)[4b] was oxidized more easily by **1** to give 4-methylbenzyl alcohol (**15**) and 4-methylbenzaldehyde (**16**) in 73 and 25% yields (after 2 h), respectively. A trace amount of 4,4′-dimethyldibenzyl (**17**) was also obtained. The oxygenation of mesitylene (**18**) ($E^{ox}_{1/2}=2.11$ V *vs.* SCE)[4b] by **1** gave 3,5-dimethylbenzyl alcohol (**19**) (69%) and 3,5-dimethylbenzaldehyde (**20**) (21%).[9]

In the case of durene (**21**) ($E^{ox}_{1/2}=1.83$ V *vs.* SCE),[4b] the corresponding oxygenated products, 2,4,5-trimethylbenzyl alcohol (**22**) (70%) and 2,4,5-trimethylbenzaldehyde (**23**) (22%),[9] were obtained.

Figure 1 shows a linear relationship between the relative consumption rates of **1** (log $k/k_{toluene}$) in the oxygenation of the methylbenzenes, **10**, **14**, **18**, and **21**, by **1** and the oxidation potentials ($E^{ox}_{1/2}$) of the methylbenzenes employed.

Weak CT bands [around 401 ($\varepsilon=3$—10) nm] between **1** and the methylbenzenes, **14**, **18**, and **21**, were observed in the difference UV-visible absorption spectra of the mixtures of **1** and the methylbenzenes *vs.* **1**.

When the reaction of **1** with **14** at 135 °C in the dark was carried out under an oxygen atmosphere for 2 h, the oxygenated products, **15** and **16**, were obtained in 116 and 224% yields based on the employed **1**, and **1** was recovered in *ca.* 99% yield. This observation implies that in the presence of oxygen the *N*-oxide **1** functions only as an electron acceptor but not as an oxygen-atom donor. Thus, the operation of the SET mechanism is also possible in the thermal oxygenation of the methylbenzenes by **1**.[10]

We propose a reaction sequence for the present thermal oxygenation of aromatic hydrocarbons by **1** as outlined in Chart 2 (a and b), by using as examples the cases of **4** and **10**.

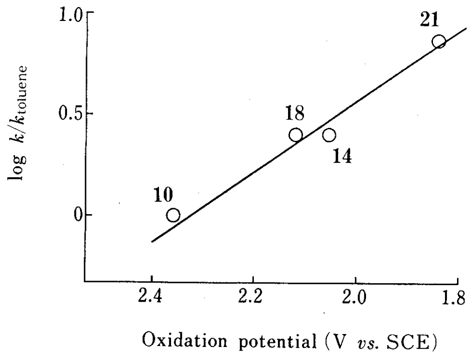

Fig. 1. Correlation between the Relative Consumption Rates of the *N*-Oxide **1** (log $k/k_{toluene}$) in the Thermal Oxygenation of the Methylbenzenes (**10**, **14**, **18**, and **21**) by **1** and the Oxidation Potentials ($E^{ox}_{1/2}$) of the Methylbenzenes Employed

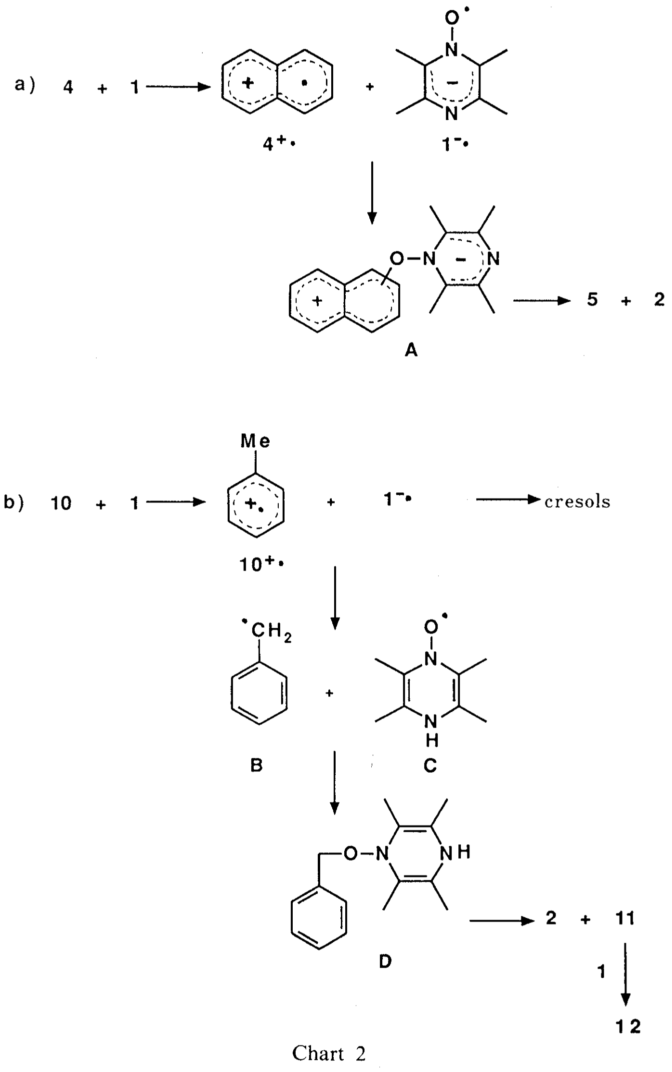

Chart 2

The SET from **4** to **1** probably occurs *via* the initial CT-complex formation to give a pair of radical ions, ($\mathbf{4}^{+\cdot}$ and $\mathbf{1}^{-\cdot}$). The transient zwitterionic intermediate (A) formed by coupling of $\mathbf{4}^{+\cdot}$ with $\mathbf{1}^{-\cdot}$ collapses to produce **5** and **2** (see a in Chart 2).[11]

In the case of **10** (see b in Chart 2), deprotonation of the cation radical $\mathbf{10}^{+\cdot}$ generated as a result of the SET from **10** to **1** exclusively takes place under thermal conditions to give the benzyl radical (B) in preference to the coupling with $\mathbf{1}^{-\cdot}$ leading to the formation of the cresols, which mainly occurs under photochemical conditions.[2]

Exergonic deprotonation of the methylbenzene cation-radicals to generate the corresponding benzyl radicals is frequently encountered in the thermal reactions of methylbenzenes involving the SET process.[12] The detection of **13** in the reaction of **10** with **1** provides evidence supporting the generation of B during the reaction.

Coupling of B with a nitroxyl radical (C) gives a transient intermediate (D), which leads to **11** and **2**. Further dehydrogenation of **11** by **1** proceeds *via* the analogous SET process to give **12**. Independent experiments showed that the dehydrogenation of **11** to give **12** takes place gradually in the presence of **1** or **2** under conditions analogous to those in the case of the oxygenation of **10**.

In conclusion, the present results provide the first example demonstrating that a heterocyclic *N*-oxide can behave as an electron acceptor and subsequently as an oxygen-atom donor under thermal conditions.

Experimental

Spectroscopic measurements for the structural assignment of the reaction products were performed with the following instruments: UV-visible absorption spectra with Shimadzu 260 spectrophotometer; proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL JNX 270 (270 MHz) spectrometer using tetramethylsilane as an internal standard; mass spectra (MS) with a JEOL JMS-D 300 machine operating at 70 eV. Gas liquid chromatography (GLC) analyses were performed with a Shimadzu GC-8APF instrument equipped with a column of 5% polyethyleneglycol (PEG) on Uniport HP (1.2 m × 3.0 mm). Thin layer chromatography analyses were carried out on Silica gel 60 plates (Merck, art. 5721) by using benzene–ethyl acetate (5 : 2) as an eluent. TLC scanning was done with a Shimadzu CS-9000 dual-wavelength flying-spot scanner for the assay of **1** and **2** (detection: 370 nm). Column chromatography was accomplished by using silica gel (Wakogel C-300).

Thermal Oxygenation of Benzene, Naphthalene (4), and Phenanthrene (6) by 1,3,6,8-Tetra-*n*-butylpyrimido[5,4-*g*]pteridine-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-tetrone 10-Oxide (1) For Benzene: A degassed solution of benzene (0.89 ml, 10 mmol) in dry acetonitrile (5.0 ml) containing **1** (12.2 mg, 0.025 mmol) was heated in a sealed tube at 135 °C in the dark for 1 d. TLC and gas chromatography (GC) analyses of the reaction mixture showed almost quantitative recovery of **1** (by TLC densitometry, *Rf* 0.27) and no detectable formation of phenol. When the reaction of benzene (5 ml) with **1** (12.2 mg, 0.025 mmol) was carried out without solvent, the formation of the expected phenol (5% yield based on the employed **1**, by GC and GC-mass) and 1,3,6,8-tetra-*n*-butylpyrimido[5,4-*g*]pteridine-2,4,5,7-(1*H*,3*H*,6*H*,8*H*)-tetrone (**2**) (*ca.* 13% yield, by TLC, *Rf* 0.35) was observed along with 87% recovery of **1**.

For **4**: A solution of **4** (1.281 g, 10 mmol) in dry acetonitrile (5.0 ml) containing **1** (12.2 mg, 0.025 mmol) was heated under conditions similar to those used in the foregoing case. TLC and GC analyses of the reaction mixture obtained after 1 d showed 40% consumption of **1** (converted into **2**) and the formation of naphthols (**5**) (as a mixture of 1- and 2-isomers with a ratio of 7 : 1, by GC and GC-mass) in 18% yield based on the employed **1**.

For **5**: A mixed solution of **5** (7.128 g, 40.0 mmol) and **1** (488 mg, 1.0 mmol) in dry acetonitrile (200 ml) was heated under conditions similar to those used in the foregoing case. The assay of the reaction mixture by TLC densitometry showed complete consumption of **1** and quantitative conversion into **2**. After removal of the solvent under reduced pressure, the resulting residue was subjected to column chromatography [eluent: *n*-hexane–benzene (5 : 2) and then benzene] to give 9-phenanthrol (**7**) (8 mg, 4% yield based on the employed **1**), bis(9-hydroxyphenanthren-10-yl) (**8**) (77 mg, 20%), and 9,10-phenanthrenedione (**9**) (35 mg, 17%). The structures of these products were confirmed by examination of the mass spectra and by comparison of their ^{1}H-NMR spectra with those of the respective authentic samples prepared from **5** by treatment with ferric chloride or by autoxidation.[6]

Thermal Oxygenation of Toluene (10), *p*-Xylene (14), Mesitylene (18), and Durene (21) by 1 A degassed solution of **1** (12.2 mg, 0.025 mmol) in **10**, **14**, **18**, or **21** (5.0 ml) was heated in a sealed tube at 135 °C in the dark. TLC and GC analyses showed smooth conversion of **1** into **2** and the formation of the corresponding benzyl alcohols, benzyl alcohol (**11**), 4-methylbenzyl alcohol (**15**), 3,5-dimethylbenzyl alcohol (**19**), or 2,4,5-trimethylbenzyl alcohol (**22**), and benzaldehydes, benzaldehyde (**12**), 4-methylbenzaldehyde (**16**), 3,5-dimethylbenzaldehyde (**20**), or 2,4,5-trimethylbenzaldehyde (**23**). The yields of these products were as follows. Products (yield based on the employed **1**): **11** (68%) and **12** (18%) from **10** (after 1 d); **15** (73%) and **16** (25%) from **14** (after 2 h); **19** (69%) and **20** (21%) from **18** (after 2 h); **22** (70%) and **23** (22%) from **21** (after 2 h). In the cases of **10** and **14**, trace amounts of the corresponding dibenzyls, dibenzyl (**13**) and 4,4′-dimethyldibenzyl (**17**), were detected in the respective reaction mixtures and their structures were confirmed by comparison of their GC retention times and GC-mass spectral data with those of authentic samples.[9]

Thermal Reaction of 4 and 10 with ^{18}*O*-Labeled *N*-Oxide (3) A solution of **4** (1.281 g, 10 mmol) and **3** (12.2 mg, 0.025 mmol; ^{18}*O*-content: 29%)[5] in dry acetonitrile (5.0 ml) was heated in a degassed sealed tube at 135 °C for 1 d. The ^{18}*O*-content of the product **5** was estimated to be *ca.* 30% by GC-mass spectrometry. In the reaction of **10** with **3**, the ^{18}*O*-content of **11** was *ca.* 30%.

Thermal Reaction of 10 with 3-Methylpyridazine 2-Oxide A solution of **10** (5.0 ml) containing 3-methylpyridazine 2-oxide (2.7 mg, 0.025 mmol) was heated under conditions similar to those used in the case of **1**. Analysis of the mixture by GC showed the recovery of the *N*-oxide employed and no formation of detectable amounts of oxidation products, **11**, **12**, and **13**.

Measurement of Relative Consumption Rates of 1 in Thermal Reaction with the Methylbenzenes, 10, 14, 18, and 21 A degassed solution of **1** (12.2 mg, 0.025 mmol) in **10**, **14**, **18**, or **21** (5 ml) was heated in a sealed tube at 135 °C in the dark. Consumption of **1** in this reaction was followed spectrophotometrically with a TLC scanner and rate constants 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 reaction for *t* min). The relative consumption rates of **1** ($\log k/k_{\text{toluene}}$) based on the case of **10** are plotted in Fig. 1 as a function of the oxidation potentials ($E^{\text{ox}}_{1/2}$, V *vs.* SCE) of the methylbenzenes employed.

CT Interaction between 1 and the Aromatic Hydrocarbons, 4, 6, 14, 18, and 21 CT complex formation between **1** and the aromatic hydrocarbons was evidenced by the difference UV-visible absorption spectra of the mixtures of **1** (5 mM) and the aromatic hydrocarbons (10 mM) *vs.* **1** (5 mM) in dry acetonitrile. The observed CT bands were as follows: 405 ($\varepsilon = 10$) nm for **1** and **4**; 405 ($\varepsilon = 16$) nm for **1** and **6**; 401 ($\varepsilon = 3$) nm for **1** and **14**, 401 ($\varepsilon = 3$) nm for **1** and **18**; 401 ($\varepsilon = 10$) nm for **1** and **21**.

Thermal Reaction of 1 with 14 under Oxygen The solution of **1** (12.2 mg, 0.025 mmol) in **14** (5.0 ml) was heated under an oxygen atmosphere in a sealed tube at 135 °C for 2 h in the dark. TLC and GC analyses of the reaction mixture showed *ca.* 99% recovery of **1** and the formation of **15** and **16** in 116 and 224% yields, respectively, based on the employed **1**.

Thermal Reaction of 11 with 1 or 2 A degassed solution of **11** (5.4 mg, 0.05 mmol) in dry acetonitrile (5.0 ml) containing **1** (12.2 mg, 0.025 mmol) was heated in a sealed tube at 135 °C for 1 d in the dark. GC analysis of the resulting reaction mixture showed the formation of **12** in 22% yield based on the employed **1**. Employment of **2** (11.8 mg, 0.025 mmol) in place of **1** resulted in the formation of **12** in 20% yield.

References and Notes

1) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *J. Am. Chem. Soc.*, **108**, 6039 (1986); Y. Maki, I. Oyabu, S. Ohara, M. Sako, Y. Kitade, and K. Hirota, *Chem. Pharm. Bull.*, **37**, 3239 (1989); Y. Maki, M. Sako, T. Murase, Y. Kitade, and K. Hirota, *Heterocycles*, **30**, 279 (1990) and preceding papers cited therein. For the preparation of the *N*-oxide **1**, see E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, **37**, 1601 (1972).

2) M. Sako, S. Ohara, K. Shimada, K. Hirota, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 863.

3) For a review, see "Chemistry of the Heterocyclic *N*-Oxides," ed. by A.

R. Katritzky and J. M. Logowski, Academic Press, New York, 1971, pp. 166—230.

4) *a*) T. Kubota, B. Uno, K. Kano, T. Kawakita, and M. Goto, *Bull. Chem. Soc. Jpn.*, **63**, 516 (1990); *b*) V. D. Parker, *J. Am. Chem. Soc.*, **98**, 98 (1976); C. J. Schlesener, C. Amatore, and J. K. Kochi, *ibid.*, **106**, 3567 (1984).

5) The ^{18}O-labeled *N*-oxide **3** was prepared by lead tetraacetate oxidation of 6-amino-5-^{18}O labeled nitroso-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione, which can be obtained with ease by the reaction of 6-amino-1,3-dibutylpyrimidine-2,4(1*H*,3*H*)-dione with nitrosonium tetrafluoroborate in THF containing $H_2{}^{18}O$.

6) F. Toda, K. Tanaka, and S. Iwata, *J. Org. Chem.*, **54**, 3007 (1989); T.-L. Ho, T.-W. Hall, and C. M. Wong, *Synthesis*, **1973**, 206.

7) M. Sako, S. Ohara, K. Hirota, and Y. Maki, *Chem. Pharm. Bull.*, **38**, 2676 (1990).

8) H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull.*, **16**, 767 (1968); T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, **1969**, 2747.

9) A. G. Gonzalez, L. M. Aguiar, J. D. Martin, and M. L. Rodriguez, *Tetrahedron Lett.*, **3**, 205 (1976).

10) Rastetter *et al.* have reported that 8-demethylflavin N_5-oxide oxygenates phenolates at ambient temperature in the dark to give the corresponding quinones *via* the phenoxy radical formed as a result of the initial SET from the phenolates to the *N*-oxide. [J. W. Frost and W. H. Rastetter, *J. Am. Chem. Soc.*, **103**, 5242 (1981)].

11) Recently, it has been pointed out that arene cation radicals give the corresponding arene radicals as a result of deprotonation by a base [*cf.* B. Reitstoen and V. D. Parker, *J. Am. Chem. Soc.*, **112**, 4968 (1990)]. Accordingly, there may be an alternative pathway involving the deprotonation of $\mathbf{4}^{+\cdot}$ by $\mathbf{1}^{-\cdot}$ to give 1- or 2-naphthyl radical and C which couple with each other and then collapse to produce **5** and **2**.

12) For a review, see L. Eberson, "Electron Transfer Reactions in Organic Chemistry," Springer-Verlag, 1987.