[Chem. Pharm. Bull. 36(5)1714—1720(1988)]

Photochemical Oxidation of 4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (Emorfazone) by Pyrimido[5,4-*g*]pteridine 5-Oxide. An Attempt to Apply a Functional Chemical Model for Biological Oxidations to Drug-Metabolism Studies[1)]

YOSHIFUMI MAKI,* KAORU SHIMADA, MAGOICHI SAKO, YUKIO KITADE, and KOSAKU HIROTA

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

(Received October 22, 1987)

Irradiation of 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**2**) (Emorfazone) with ultraviolet (UV)-visible light in the presence of 1,3,7,9-tetrabutyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido-[5,4-*g*]pteridinetetrone 5-oxide (**1a**), followed by chromatography of the reaction mixture, resulted in the isolation of 5-(2,3-dihydro-1,4-oxazin-4-yl)-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (**3**), 4-ethoxy-5-(2-hydroxyethylamino)-2-methyl-3(2*H*)-pyridazinone (**4**), 4-ethoxycarbonyl-2-methyl-4-morpholino-3(2*H*)-pyrazolone (**5**), 4,4′-bi[4-ethoxycarbonyl-2-methyl-3(2*H*)-pyrazolone] (**6**) and 1,3,7,9-tetrabutyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridinetetrone (**1b**). The product **3** is produced as a result of photochemical dehydrogenation of **2** by **1a**. The formation of the morpholine-ring-opening product **4**, one of the metabolites of **2**, was proved to occur *via* the autoxidation of **3** and subsequent stepwise ring cleavage in the presence of oxygen and moisture. The formation of the novel ring-contracted product **5** involves oxygen-atom transfer from **1a** to **2** in an excited state. The dimer **6** was shown to be a secondary product formed by further photolysis of **5**.

Keywords——photo-oxidation; 5-morpholino-3(2*H*)-pyridazinone; pyrimidopteridine 5-oxide; oxygenation; dehydrogenation; ring contraction; single-electron transfer

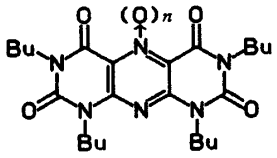
Photochemical oxygen-atom transfer reaction by heterocyclic *N*-oxides has been considered to be one of the functional chemical models for a variety of biological oxidations catalyzed by hepatic monooxygenases, *e.g.*, cytochrome P-450. After extensive investigations, it has been proposed that the oxygen-atom transfer reaction is induced by active oxygen species such as an oxene or an oxazilidine intermediate arising from the excited *N*-oxides.[2)] The complicated photochemical reactivities of the *N*-oxides so far employed in these investigations, however, have made it difficult to transfer efficiently an oxygen atom from the *N*-oxides to the substrates.[3)]

During our search for the heterocyclic *N*-oxides which could serve as efficient oxygen-atom transfer agents without undesirable photoreactions such as intramolecular rearrangements, our attention was directed toward the 2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]-pteridinetetrone 5-oxide system (*cf.* **1a**) prepared by us through two simple synthetic routes.[4)]

The special structural feature of the pyrimido[5,4-*g*]pteridine 5-oxide system is that the *N*-oxide function is uniquely situated between two adjacent carbonyl groups and on the electron-deficient pyrazine ring annelated on both sides by the electron-accepting uracil ring.[5)]

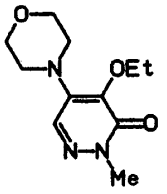
1,3,7,9-Tetrabutyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridinetetrone 5-oxide (**1a**) was chosen as a target by considering the solubility in organic solvents, among various alkyl derivatives of this system.

In accordance with our expectation, **1a** has been proved to cause an efficient oxygen-



1a: n = 1
1b: n = 0

Chart 1



2

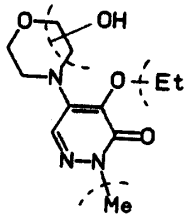


Fig. 1. Outline of the Metabolism of 4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**2**)

atom transfer to substrates under photochemical conditions without any appreciable side reactions, *i.e.*, the *N*-oxide (**1a**) efficiently oxidized benzenes,[6] *N*,*N*-dimethylaniline,[7] thioanisole, dibenzyl ether and *trans*-stilbene[8] under irradiation with ultraviolet (UV)-visible light to give the corresponding oxidized products (*e.g.*, phenols, *N*-monomethylaniline, thioanisole sulfoxide, benzyl alcohol and *trans*-stilbene oxide). Tryptophan derivatives also underwent photooxidative C_α–C_β bond cleavage of their side-chains under certain conditions.[9]

These photochemical oxidations can be rationalized by a combination of single-electron transfer (SET) and subsequent oxygen-atom transfer taking place between **1a** and the substrates, which suggests the presence of an alternative process not involving the active oxygen species proposed previously in the photochemical oxidation by the heterocyclic *N*-oxides. It is worthwhile to note that the oxidation mode mechanistically parallels that proposed for an oxo-iron(IV) porphyrin cation radical, an active species in the cytochrome P-450-catalyzed oxidation.[10]

Another mode of photochemical oxidation by **1a** is its behavior as an efficient agent for dehydrogenation: the *N*-oxide (**1a**) caused the photochemical formation of 8,5′-*O*-cyclopurine nucleosides starting from purine nucleosides,[11] the oxidative photo-cyclization of N^6-benzoyladenosines to quinazolinopurine nucleosides,[12] and the photo-oxidative conversion of 2′-hydroxychalcones into flavones.[13]

These photo-dehydrogenations can be explained in terms of an initial SET from the substrates to **1a** and subsequent capture of a proton and a hydrogen by the resulting anion radical of **1a** without oxygen atom transfer, which is formally oxidase- or dehydrogenase-like.

The multifunctionality and efficiency of **1a** in the photo-oxidation as demonstrated previously led us to direct our attention to their application to the oxidation of some drugs. These investigations may lead to the discovery of new metabolites of the drugs and play a complementary role to studies on the drug metabolism.

Along this line, we attempted the photo-oxidation of 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**2**) (Emorfazone), which has been developed by Morishita Pharmaceutical Co., Ltd. and one of the authors (Y.M.), and is used clinically as an analgesic-antiinflammatory agent.[14] Although there is a species difference in the metabolism of Emorfazone (**2**), it has been documented that the primary metabolic feature is ring cleavage of the morpholine moiety, possibly involving an initial hydroxylation and subsequent stepwise oxidations, and this is accompanied with *N*-demethylation and *O*-deethylation[15,16] (see Fig. 1).

This paper describes the results of photo-oxidation of **2** by **1a**, demonstrating that **1a** behaves as an efficient agent for both dehydrogenation and oxygenation. A present finding is suggestive of the presence of an alternative to the metabolic pathway proposed previously for the oxidative cleavage of the morpholine ring in **2**.[15] Occurrence of a novel type of photooxidative ring contraction of **2** by **1a** is intriguing from the mechanistic viewpoint.

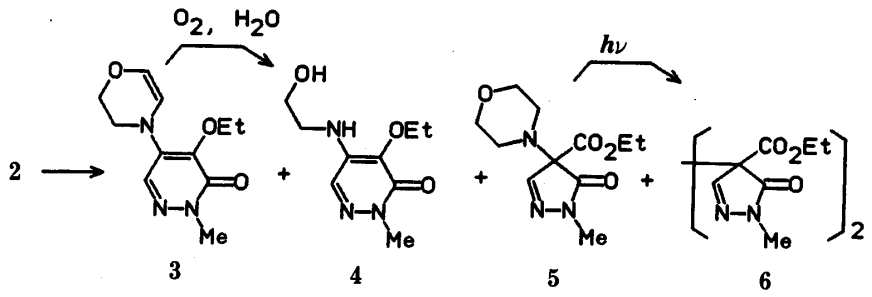


Chart 2

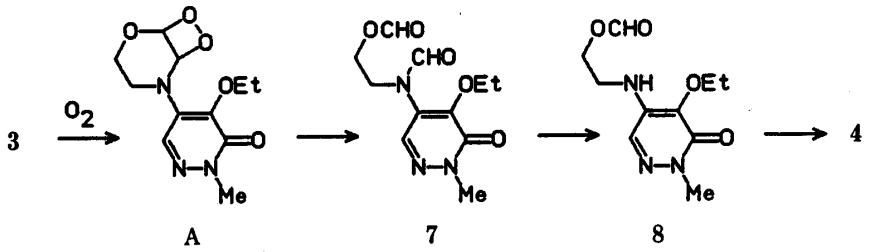


Chart 3

Results and Discussion

A solution of **2** (4 mM) in acetonitrile in the presence of **1a** (2 mM) was irradiated with a 400W high-pressure mercury arc lamp through a Pyrex filter under argon for 0.5 h. The thin-layer chromatographic (TLC) analysis of the irradiated solution showed the presence of at least four compounds in addition to the deoxygenated pyrimido[5,4-*g*]pteridine (**1b**) and the unchanged starting material **2**. Careful chromatographic separation of the residue after evaporation of the solvent resulted in the isolation of 5-(2,3-dihydro-1,4-oxazin-4-yl)-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (**3**) (14%), 4-ethoxy-5-(2-hydroxyethylamino)-2-methyl-3(2*H*)-pyridazinone (**4**) (2%), 4-ethoxycarbonyl-2-methyl-4-morpholino-3(2*H*)-pyrazolone (**5**) (28%), 4,4′-bi[4-ethoxycarbonyl-2-methyl-3(2*H*)-pyrazolone] (**6**) (30%) and **1b** (91%).

The structural proof of **3** rests upon its spectral data and chemical conversion into **4**. The mass spectrum (MS) of **3** exhibited a parent peak (*m/z*: 237), which is less by *m/z*: 2 than that of **2**. The proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra of **3** supported the presence of two olefinic protons [δ: 6.09 (1H, d, 4.8 Hz), 5.88 (1H, d, 4.8 Hz)] and of two sp^2 carbons [δ: 109.03 (d), 129.76 (d)] in the morpholine ring. The product **3** was fairly sensitive to autoxidation in agreement with the previous observation[17] in 2,3-dihydro-1,4-oxazines. Exposure of **3** in acetonitrile to air gave a complicated mixture of degraded products, from which **4** was isolated by silica gel chromatography. The degraded product **4** thus obtained was identical in every respect with an authentic sample prepared independently.

The oxidative degradation of **3** leading to **4** can be explained in terms of a possible intermediacy of dioxetane (A), which undergoes with ease the ring cleavage and subsequent hydrolysis by moisture in the medium to give **4** (see Chart 3). In fact, the intermediary products, the *N,O*-diformyl derivative (**7**) and the *O*-formyl derivative (**8**), were isolated from the reaction mixture in the autoxidation of **3** and characterized. Thus, the formation of **4** arises from the autoxidative degradation of **3** in the ground-state, which occurs during the post-treatment rather than the photochemical process.

The structures of the novel ring-contracted products **5** and **6** were confirmed on the basis

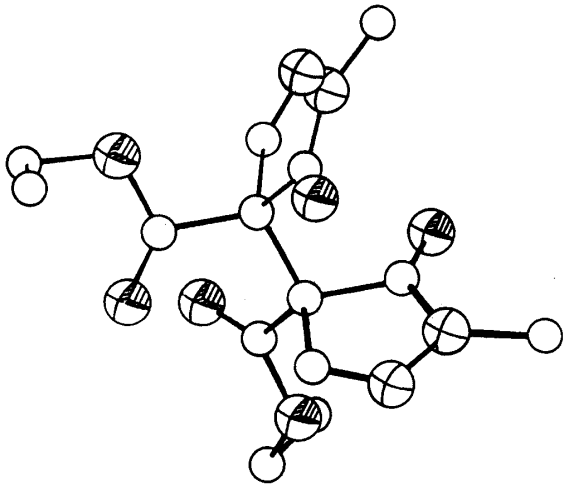


Fig. 2. ORTEP View of 4,4′-Bi[4-ethoxycarbonyl-2-methyl-3(2*H*)-pyridazinone] (**6**)

of their spectral data, the chemical reactivities of **5**, and an X-ray crystallographic analysis of **6**.

The MS and microanalytical results in the case of **5** showed the insertion of an oxygen atom into **2** by **1a**. The UV spectrum of **5** [λ_{max}^{MeCN} nm (log ε): 266 (3.43)] was evidently different from that of **2** [λ_{max}^{MeCN} nm (log ε): 314 (3.76), 294 (3.77)], indicating a drastic transformation of the parent 3(2*H*)-pyridazinone ring in **2**. The presence of an ethoxycarbonyl group in **5** was supported by its infrared spectrum (IR) [ν_{max}^{KBr} cm^{-1}: 1760 (ester carbonyl)] and ^{13}C-NMR spectrum [δ: 163.90 (ester carbonyl carbon)], and by its conversion into methylamide, [IR ν_{max}^{KBr} cm^{-1}: 1675 (amide carbonyl)] (see Experimental section).

Analogous irradiation of **5** in the absence of **1a** gave the dimer **6** in 90% yield. The structure of **6** was deduced from its spectral data and microanalytical results, and was conclusively confirmed by an X-ray crystallographic study[18] (see Fig. 2).

The above result indicates unequivocally that the dimer **6** is formed as a result of further photoreaction of **5**, which is accounted for by homolytic cleavage of the *C–N* bond at the quaternary carbon (C-4) in **5** and coupling of the resulting carbon radical. As a consequence, the structure of **5** was established.

The base-catalyzed ring contraction of 3(2*H*)-pyridazinone derivatives to give 3(2*H*)-pyrazolone-4-carboxylic acid derivatives has been studied.[19] The photo-oxidative ring contraction of the 3(2*H*)-pyridazinones, however, is unprecedented.

The reaction modes for the formation of these products **3** and **5**, the primary photoproducts of **2** under the influence of **1a**, can be outlined as depicted in Chart 4.

The difference spectrum (λ_{max}^{MeCN}: 424 nm) of a mixture of **2** and **1a** *vs.* **1a** [λ_{max}^{MeCN} nm (log ε): 370 (4.34), 270 (4.70), 242 (4.51)] in acetonitrile showed the presence of a charge-transfer interaction between **1a** and **2** in the ground state. A marked wavelength dependence was observed for the formation of **5**, and excitation of the charge-transfer complex with 424 nm light resulted in a maximum yield of **5**, as demonstrated previously in the photo-oxidative *N*-demethylation of dimethylaniline by **1a**.[7] Irradiation of **2** in the presence of tetracyanoquinodimethane, a typical electron acceptor, in place of **1a** also gave **3**, although the yield was unsatisfactory.[20,21] Thus, the present photoreactions could be initiated by the SET from **2** to **1a** in an excited state.[22]

The *N*-oxide anion radical (B) thus formed could capture a proton from the Emorfazone cation radical (C) to generate radical species (D) and (E). Efficient hydrogen abstraction from E by D produces **3** and the intermediate (F) which gives **1b** as a result of elimination of water.

The formation of the ring-contracted product **5** can be explained by coupling of the anion radical B with the cation radical C in the solvent cage, leading to intermediacy of G, followed

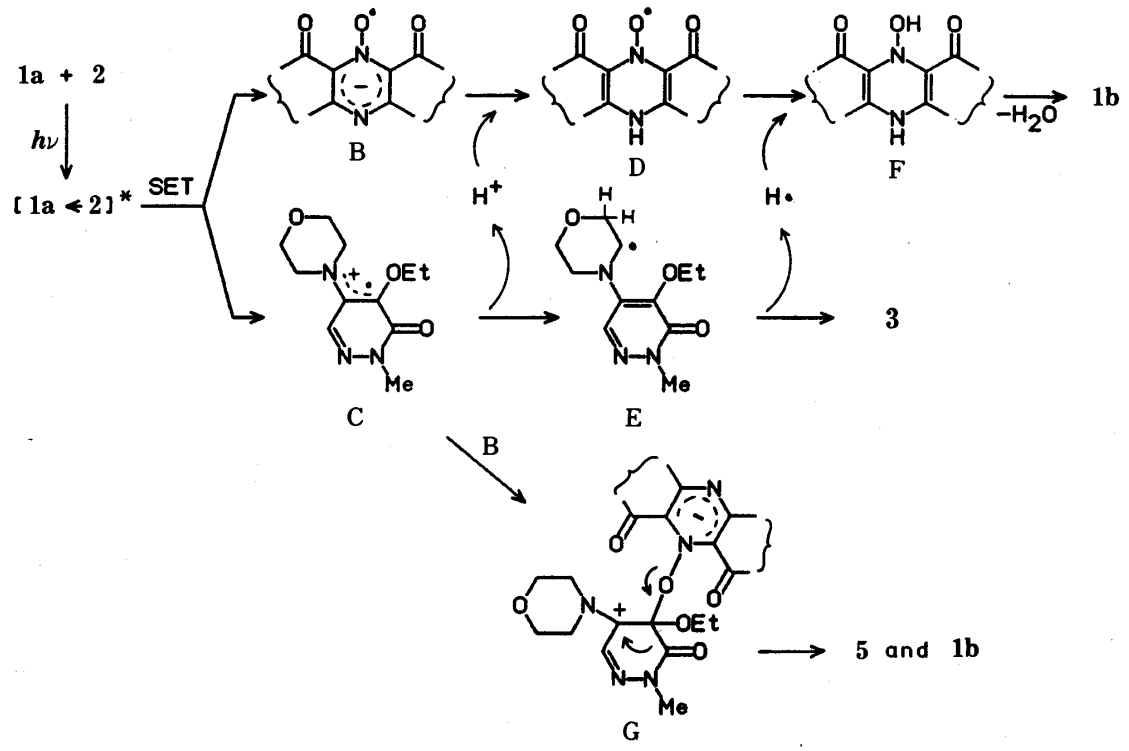


Chart 4

by ring contraction.[23] Thus, the oxygen atom in the *N*-oxide **1a** is incorporated into the ester carbonyl oxygen of **5**.

As mentioned at the beginning of this article, the *N*-oxide **1a** behaves as an efficient oxygen-atom transfer agent (functionally monooxygenase-like) as well as an oxidant for dehydrogenation (functionally oxidase- or dehydrogenase-like) under the photochemical conditions, largely depending upon the nature of the substrates employed. In the present photochemical reactions, both characteristics of **1a** play significant roles in the oxidation of **2**: the formation of **3** originates from the capacity of **1a** for dehydrogenation, while **5** is produced owing to its function for oxygen-atom transfer.

The metabolism of **2** yields ten identified metabolites, most of which arise from the stepwise oxygenative degradation of the morpholine moiety on the way to the ultimate metabolite **4**.[15] Careful inspection of a thin-layer chromatogram of the irradiated solution (*vide supra*), using authentic samples of the metabolites[15,24] as reference standards, did not show the presence of photo-products corresponding to the metabolites except for **4**. The present experiment clearly indicates that the formation of **4** occurs thermally *via* the olefinic product **3**, which is suggestive of the presence of a metabolic pathway involving the initial formation of **3** in the degradation of the morpholine ring in **2** leading to **4**.

The oxidative ring-contracted product **5** has never been identified as a metabolite of **2**. Although the reaction mode for the generation of the transient intermediate G in advance of the ring contraction is formally analogous to that of the oxidation of some substrates by the oxo-iron(IV)porphyrin cation radical,[10] the ring-contraction step in G seems to occur only under photochemical conditions (see Chart 4).

The photochemical oxidation of the substrates by heterocyclic *N*-oxides such as **1a** can be regarded as a simple functional chemical model for oxygenases and oxidases or dehydrogenases, and is apparently different from the sophisticated enzymatic reactions in the ground state. This type of simple photo-oxidation, however, provides some complementary information for comparison with the biochemical oxidation of xenobiotics and physiological substances, and may be applicable to some extent for the chemical modification of drugs.

Experimental

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Irradiation was carried out under an argon atmosphere by using a 400W high-pressure mercury arc lamp (Riko Kagaku Sangyo) through a Pyrex filter. A JASCO CRM-FA spectroirradiator (2 kW Xe lamp) was used for the wavelength-dependence experiment. IR spectra were recorded on a Hitachi 215 spectrometer and UV spectra on a Shimadzu 260 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured with a JEOL JNX-270 spectrometer using tetramethylsilane as an internal standard. MS were taken on a JEOL JMS-D300 machine operating at 70 eV. Microanalyses were performed in the Microanalytical Laboratory of our university. Column chromatographic separation was accomplished by using silica gel (Wakogel C-100). Preparative TLC (PTLC) and TLC were performed on Silica gel 60 plates (Art 5717 and 5721, Merck Co., Ltd.). TLC scanning was performed on a Hitachi 556 spectrophotometer with a TLC densitometer.

Photochemical Oxidation of 4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (Emorfazone) (2) with 1,3,7,9-Tetrabutyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridinetetrone 5-Oxide (1a)——A solution of **2** (957 mg, 4 mmol) and **1a** (977 mg, 2 mmol) in dry MeCN (1000 ml) was irradiated at room temperature for 0.5 h. The residue obtained after evaporation of the solvent was chromatographed on silica gel as quickly as possible. Elution with $CHCl_3$–MeOH (60 : 1) gave 4,4′-bi[4-ethoxycarbonyl-2-methyl-3(2*H*)-pyrazolone] (**6**) (102 mg, 30%), 4-ethoxycarbonyl-2-methyl-4-morpholino-3(2*H*)-pyrazolone (**5**) (142 mg, 28%), 5-(2,3-dihydro-1,4-oxazin-4-yl)-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (**3**) (66 mg, 14%), and 4-ethoxy-5-(2-hydroxyethylamino)-2-methyl-3(2*H*)-pyridazinone (**4**) (8.5 mg, 2%), together with 1,3,7,9-tetrabutyl-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-pyrimido[5,4-*g*]pteridinetetrone (**1b**) (857 mg, 91%), and unchanged **2** (458 mg).

3: mp 58—61 °C. UV λ_{max}^{MeCN} nm (log ε): 347 (3.73), 258 (4.15), 213 (4.09). IR ν_{max}^{KBr} cm^{-1}: 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, *J* = 7.0 Hz), 3.72 (3H, s), 3.78 (2H, t, *J* = 4.4 Hz), 4.13 (2H, t, *J* = 4.4 Hz), 4.27 (2H, q, *J* = 7.0 Hz), 5.88 (1H, d, *J* = 4.8 Hz), 6.09 (1H, d, *J* = 4.8 Hz), 7.61 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 15.47 (q), 39.57 (q), 46.44 (t), 65.07 (t), 67.91 (t), 109.03 (d), 128.35 (s), 129.76 (d), 131.30 (d), 135.48 (s), 159.26 (s). MS *m/z*: 237 (M^+).

4: mp 101 °C (EtOH, lit.[24] 100—101 °C).

5: mp 87 °C (Et_2O). UV λ_{max}^{MeCN} nm (log ε): 266 (3.43). IR ν_{max}^{KBr} cm^{-1}: 1760, 1710. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J* = 7.0 Hz), 2.69 (1H, m), 2.95 (1H, m), 3.34 (3H, s), 3.76 (4H, t, *J* = 4.5 Hz), 4.27 (2H, q, *J* = 7.0 Hz), 7.31 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 13.92 (q), 31.42 (q), 47.89 (t), 62.83 (t), 66.75 (t), 76.87 (s), 146.01 (d), 163.90 (s), 168.45 (s). MS *m/z*: 255 (M^+). *Anal.* Calcd for $C_{11}H_{17}N_3O_4$: C, 51.75; H, 6.71; N, 16.46. Found: C, 51.62; H, 6.70; N, 16.44. Methylamine (10% MeOH-solution, 2 ml) was added to a solution of **5** (128 mg) in MeOH (15 ml) at room temperature and the reaction mixture was allowed to stand for 10 min. After evaporation of the solvent, the resulting solid was recrystallized from Et_2O to give 2-methyl-4-methylcarbamoyl-4-morpholino-3(2*H*)-pyrazolone (104 mg, 87%). mp 126 °C. UV λ_{max}^{MeCN} nm (log ε): 266 (3.41), 218 (3.34). IR ν_{max}^{KBr} cm^{-1}: 3350, 1710, 1675. ^{1}H-NMR ($CDCl_3$) δ: 2.64—2.70 (4H, m), 2.86 (3H, d, *J* = 4.9 Hz), 3.33 (3H, s), 3.68—3.80 (4H, m), 7.06 (1H, br), 7.63 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 26.36 (q), 31.38 (q), 48.57 (t), 66.72 (t), 75.78 (s), 149.09 (d), 164.23 (s), 168.42 (s). *Anal.* Calcd for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 50.08; H, 6.79; N, 23.26. MS *m/z*: 240 (M^+).

6: mp 142—143 °C (Et_2O). UV λ_{max}^{MeCN} nm (log ε): 256 (3.79), 200 (4.58). IR ν_{max}^{KBr} cm^{-1}: 1750, 1715. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (6H, t, *J* = 7.0 Hz), 3.29 (6H, s), 4.14—4.34 (4H, m), 7.85 (2H, s). ^{13}C-NMR ($CDCl_3$): 13.88 (q), 31.91 (q), 63.68 (t), 64.16 (s), 146.77 (d), 163.71 (s), 165.96 (s). MS *m/z*: 338 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.67; H, 5.38; N, 16.52. Photolysis of **5** in dry MeCN under analogous conditions in the absence of **1a** gave **6** in 90% yield.

Autoxidation of 5-(2,3-Dihydro-1,4-oxazin-4-yl)-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (3)——A solution of **3** (237 mg, 1 mmol) in MeCN (30 ml) was stirred at room temperature for 3 d. After removal of the solvent, the residue was chromatographed by using $CHCl_3$–MeOH (100 : 1) as the eluent to give 4-ethoxy-5-[*N*-formyl-*N*-(2-formyloxyethyl)amino]-2-methyl-3(2*H*)-pyridazinone (**7**) (32 mg, 12%), 4-ethoxy-5-[*N*-(2-formyloxyethyl)amino]-2-methyl-3(2*H*)-pyridazinone (**8**) (60 mg, 25%), and the 5-hydroxyethylaminopyridazinone (**4**) (60 mg, 28%), together with unchanged **3** (41 mg, 17%).

7: Colorless oil. UV λ_{max}^{MeCN} nm (log ε): 292 (3.75), 279 (3.72), 229 (4.10). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1695, 1650. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, t, *J* = 7.0 Hz), 3.79 (3H, s), 3.99 (2H, t, *J* = 5.4 Hz), 4.34 (2H, t, *J* = 5.4 Hz), 4.65 (2H, q, *J* = 7.0 Hz), 7.66 (1H, s), 7.99 (1H, s), 8.23 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 15.80 (q), 40.26 (q), 43.60 (t), 61.05 (t), 69.14 (t), 128.87 (s), 135.43 (d), 148.40 (s), 158.12 (s), 160.28 (d), 162.41 (d). MS *m/z*: 269 (M^+).

8: Colorless oil. UV λ_{max}^{MeCN} nm (log ε): 308 (3.75), 285 (3.72), 228 (4.48). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1630. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, t, *J* = 7.0 Hz), 3.55 (1H, q, *J* = 5.6 Hz), 3.72 (3H, s), 4.35 (1H, t, *J* = 5.6 Hz), 4.40 (2H, q, *J* = 7.0 Hz), 4.75 (1H, br t, *J* = 5.6 Hz), 7.58 (1H, s), 8.10 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 15.75 (q), 39.51 (q), 41.73 (t), 62.29 (t), 66.56 (t), 126.78 (d), 133.49 (s), 138.50 (s), 157.75 (s), 160.66 (d). MS *m/z*: 241 (M^+).

Photoreaction of 4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (2) in the Presence of Tetracyanoquinodimethane (TCNQ)——A solution of **2** (239 mg, 1 mmol) and TCNQ (102 mg, 0.5 mmol) in dry MeCN (250 ml) was irradiated at room temperature for 4 h. After removal of the solvent, the residue was subjected to PTLC (benzene : AcOEt = 3 : 7) to give a trace amount of **3**, which was identical with the sample obtained above.

Wavelength-Dependence Experiment for the Photochemical Formation of 5 in the Presence of 1a——A solution of **2** (4 mM) and **1a** (2 mM) in MeCN was irradiated with light of various wavelengths for 3 d. The yields of **5** in these photoreactions were determined spectrophotometrically with a TLC scanner (*Rf* value = 0.55, benzene : AcOEt = 3 : 7, detector = 266 nm). The results were as follows. Yield (wavelength, nm): 0% (503), 32% (450), 64% (424, CT-band), 20% (398), 1% (345), 0% (318). The charge-transfer band (424 nm) was observed in the difference UV spectrum of the mixture of **1a** (5 mM) and **2** (500 mM) *vs.* **1a** (5 mM) in acetonitrile.

Acknowledgement The authors are indebted to Dr. K. Nakagawa and his staff, Tokushima Laboratory, Otsuka Pharmaceutical Co., Ltd. for the X-ray crystallographic study. We are also grateful to Dr. T. Yuizono, Research Laboratory, Morishita Pharmaceutical Co., Ltd. for the generous supply of authentic metabolites of Emorfazone.

References and Notes

1) This paper is dedicated to Professor Edward C. Taylor, Princeton University, on the occasion of his 65th birthday.
2) For a recent review on the photochemistry of the heterocyclic *N*-oxides, see A. Albini and M. Alpegiani, *Chem. Rev.*, **84**, 43 (1984).
3) *a*) J. Streith, B. Danner, and C. Sigwalt, *J. Chem. Soc., Chem. Commun.*, **1967**, 979; *b*) H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull.*, **16**, 767 (1968); *c*) D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, **1970**, 457; *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.*, **101**, 2228 (1979); *f*) M. N. Akhtar, D. R. Boyd, J. D. Neill, and D. M. Jerina, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1693; *g*) Y. Ogawa, S. Iwasaki, and S. Okuda, *Tetrahedron Lett.*, **22**, 2277, and 3637 (1981).
4) Y. Maki, M. Sako, and E. C. Taylor, *Tetrahedron Lett.*, **1971**, 4271; E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, **37**, 1601 (1972).
5) M. Sako, M. Suzuki, M. Tanabe, and Y. Maki, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 3114; M. Sako, K. Hirota, and Y. Maki, *Chem. Pharm. Bull.*, **31**, 3496 (1983); M. Sako, K. Hirota, and Y. Maki, *Tetrahedron*, **39**, 3919 (1983).
6) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *Tetrahedron Lett.*, **26**, 6493 (1985).
7) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *J. Am. Chem. Soc.*, **108**, 6039 (1986).
8) Y. Maki, M. Sako, K. Shimada, T. Murase, and K. Hirota, Abstracts of Papers, International Symposium on Activation of Dioxygen and Homogeneous Catalytic Oxidation, Tsukuba, Japan July, 1987, p. 59.
9) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *Tetrahedron Lett.*, **27**, 3877 (1986).
10) For a recent review on the mechanisms of cytochrome P-450 catalyzed oxidations, see F. P. Guengerich and T. L. MacDonald, *Acc. Chem. Res.*, **17**, 9 (1984).
11) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, **1986**, 1704.
12) K. Shimada, M. Sako, K. Hirota, and Y. Maki, *Tetrahedron Lett.*, **28**, 207 (1987).
13) Y. Maki, K. Shimada, M. Sako, and K. Hirota, *Tetrahedron*, in press.
14) M. Takaya, M. Sato, K. Terashima, H. Tanizawa, and Y. Maki, *J. Med. Chem.*, **22**, 53 (1979).
15) T. Hayashi, M. Aoyama, M. Fukuda, M. Ohki, and T. Kishikawa, *Chem. Pharm. Bull.*, **27**, 317 (1979).
16) For examples of biometabolism of the morpholine ring, see D. B. Hope and K. C. Horncastle, *Biochem. J.*, **102**, 910 (1967); M. Tohno, Y. Doi, N. Kajikawa, T. Ofuji, A. Tatematsu, M. Suzuki, H. Yoshizumi, and T. Nadai, *Pharmacometrics*, **14**, 289 (1977).
17) H. B. Henbest and A. Thomas, *J. Chem. Soc.*, **1957**, 3032.
18) Details of the X-ray crystallography of **6** will be reported elsewhere.
19) Y. Maki, M. Suzuki, and M. Takaya, *Chem. Pharm. Bull.*, **22**, 229 (1974) and references cited therein.
20) The low yield of **3** may be ascribed to the lower efficiency of the carbon-center radical resulting from tetracyanoquinodimethane for the subsequent hydrogen abstraction.
21) The wavelength-dependence experiment for the formation of **3** did not give a reliable result because of the lability of **3**.
22) At present, we can not completely exclude the mechanism for the formation of **3** involving direct hydrogen abstraction from the morpholine moiety of **2** by excited **1a**.
23) The formation of the corresponding 4,5-epoxide from the intermediate G followed by photochemical ring contraction is also possible. For the photochemical ring contraction of cyclic α,β-epoxyketones, see G. W. Griffin and P. Padwa, "Photochemistry of Heterocyclic Compounds," ed. by O. Buchardt, John Wiley and Sons, New York, 1976, p. 41.
24) M. Takaya, T. Yamada, and H. Shimamura, *Yakugaku Zasshi*, **98**, 1421 (1978).