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Photochemical and Thermal Behavior of 2-Benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone and Its Derivatives

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Preparation and cyclization of 2-benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone and its derivatives have been investigated. Photochemical ring-closure followed by oxidative dehydrogenation was observed in suitably fixed triene derivatives. The results suggest that the cyclization of the photoenols (trienes) of 3-alkyl substituted 2-benzoylcyclohex-2-enones to anthracenone derivatives occurs photochemically.

Keywords—synthesis of 2-benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone; photoenolization; pericyclic reaction; oxidative intramolecular cyclization; isoxazole-fixed triene; protection of 2-benzoylcyclohex-2-enone derivatives; formation of 10-ethoxycarbonyl-9-hydroxy-3,4-dihydroanthracen-1(2H)-one

Since Yang and Rivas reported¹⁾ the photoenolization of 2-substituted aromatic carbonyl compounds, a number of related photoreactions and applications have been reported by different groups.²⁾ We have also reported³⁾ the related photocyclization of 2-aryl-3-methylcyclohex-2-enones (**1**) giving 3,4-dihydroanthracen-1(2H)-ones (**3**) via the photoenols [trienes (**2**)]. However, we could not definitely determine whether the cyclization of the trienes (**2**) occurs thermally or photochemically. We have now studied the photochemical and thermal behavior of suitably 3-substituted 2-arylcyclohex-2-enone derivatives and propose here that the cyclization of the trienes (**2**) to the anthracenones (**3**) occurs photochemically.

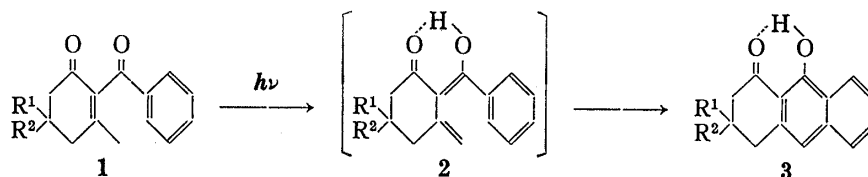


Chart 1

Results and Discussion

To obtain a more stable enol (triene) intermediates than the enol (**2**) derived from the 2-aryl-3-methylcyclohex-2-enone (**1**), we attempted to prepare a suitable enone having an electron withdrawing group such as an ethoxycarbonyl group on the 3-methyl substituent. The desired enone (**4**) was obtained by a method similar to that described for the preparation of 2-benzoyl-3-methylcyclohex-2-enone (**1**) starting with the corresponding 3-chlorocyclohex-2-enone.³⁾ Thus, treatment of 2-benzoyl-3-chlorocyclohex-2-enone with sodium ethyl *tert*-butyl malonate in dry benzene followed by thermal hydrolysis in the presence of *p*-toluene-sulfonic acid gave **4** accompanied by a small amount of the lactone (**5**).

Upon irradiation of an ether or ethanol solution of **4** in a quartz vessel, photoenolization to the enol species [*e.g.*, trienes (**6a**) and (**6b**)] occurs as in the case of 2-aryl-3-methylcyclohex-2-enone (**1**), and is followed by a cyclization and loss of hydrogen, giving the naphthol (**7**) (run 1). Addition of either a Lewis acid (runs 2 and 3) or base (run 5) to the solution

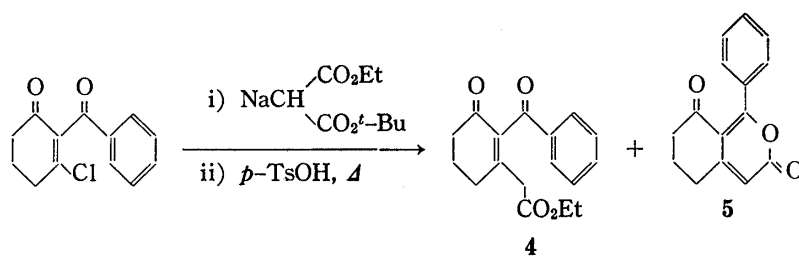


Chart 2

was found to favor the photocyclization. The results using the Lewis acid are consistent with the assumption³⁾ that the initially formed triene (**6b**) may be stabilized by coordination between the electron-deficient boron or tin atom and the oxygen atom of the C-1 carbonyl, *e.g.*, (i). The results using NaOEt arise from the stabilization of the enolate anion (ii) by conjugation with the ethoxycarbonyl group. In contrast, thermolysis of **4** both in the presence and absence of Lewis acid or base gave a complex mixture without producing the anthracene (**7**) (runs 7—9). These results are summarized in Table I. It remains uncertain whether the formation of **6b** is restricted or whether cyclization of **6b** is retarded under the thermolysis conditions.

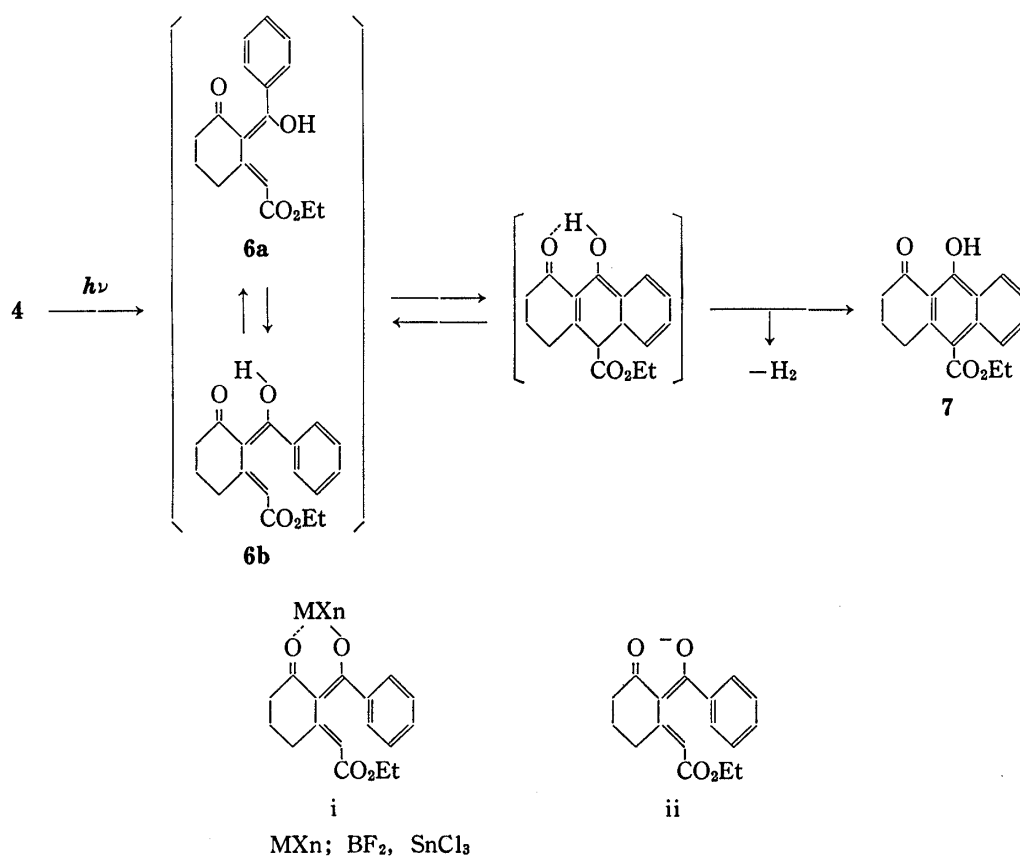


Chart 3

Therefore, we focused our attention on the photochemical and thermal behavior of suitably fixed enol derivatives of 2-benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (**4**) and planned to prepare the enol ether (**8**) and the isoxazole-fixed triene (**9**). Although the enol ether (**8**)⁴⁾ could be prepared simply by treatment of **4** with diazomethane in ether at room temperature, it proved to be unsuitable for our purpose; photochemical and thermal reactions of **8** did not occur at all in the absence of oxidizing reagent. Addition of iodine to the solution

changed the behavior, but only photochemical demethylation⁵⁾ of **8** into **4** and thermal aromatization⁶⁾ of **8** into **10** occurred. In contrast, the isoxazole-fixed triene (**9**) was quite useful, since preparation of **9** could be performed readily from **4** by the previously reported method using hydroxylamine hydrochloride in refluxing ethanol⁷⁾ and the isoxazole ring of **9** was rather stable under the photochemical and thermal conditions used. Whereas thermal

TABLE I. Photochemical and Thermal Behavior of 2-Benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (**4**)

Runs	Reaction conditions	Yields ^{a)} (%)	
		Anthracenone (7)	S.M. (4)
1	in Et ₂ O, 15°C, 40 h, <i>hν</i> ^{b)}	18	39
2	in Et ₂ O, BF ₃ -Et ₂ O, 15°C, 20 h, <i>hν</i> ^{b)}	28	39
3	in Et ₂ O-EtOH, SnCl ₄ , 15°C, 70 h, <i>hν</i> ^{b)}	33	29
4	in Et ₂ O, Et ₃ N, 15°C, 20 h, <i>hν</i> ^{b)}	19	23
5	in EtOH, EtONa, 15°C, 50 h, <i>hν</i> ^{b)}	42	Trace
6	in Et ₂ O, I ₂ , 15°C, 20 h, <i>hν</i> ^{b)}	14	28
7	in C ₆ H ₅ NO ₂ , 20 h, reflux	Complex mixture ^{c)}	
8	in C ₆ H ₅ NO ₂ , AlCl ₃ , 10 h, reflux		
9	in EtOH, EtONa, reflux		

a) Yields are those for reactions of **4** carried out on a 0.2–0.5 mmol scale in the indicated solvent (10–25 ml).

b) Irradiation was performed in a quartz vessel with a 350 W high-pressure mercury lamp.

c) Anthracenone (**7**) was not included among these compounds.

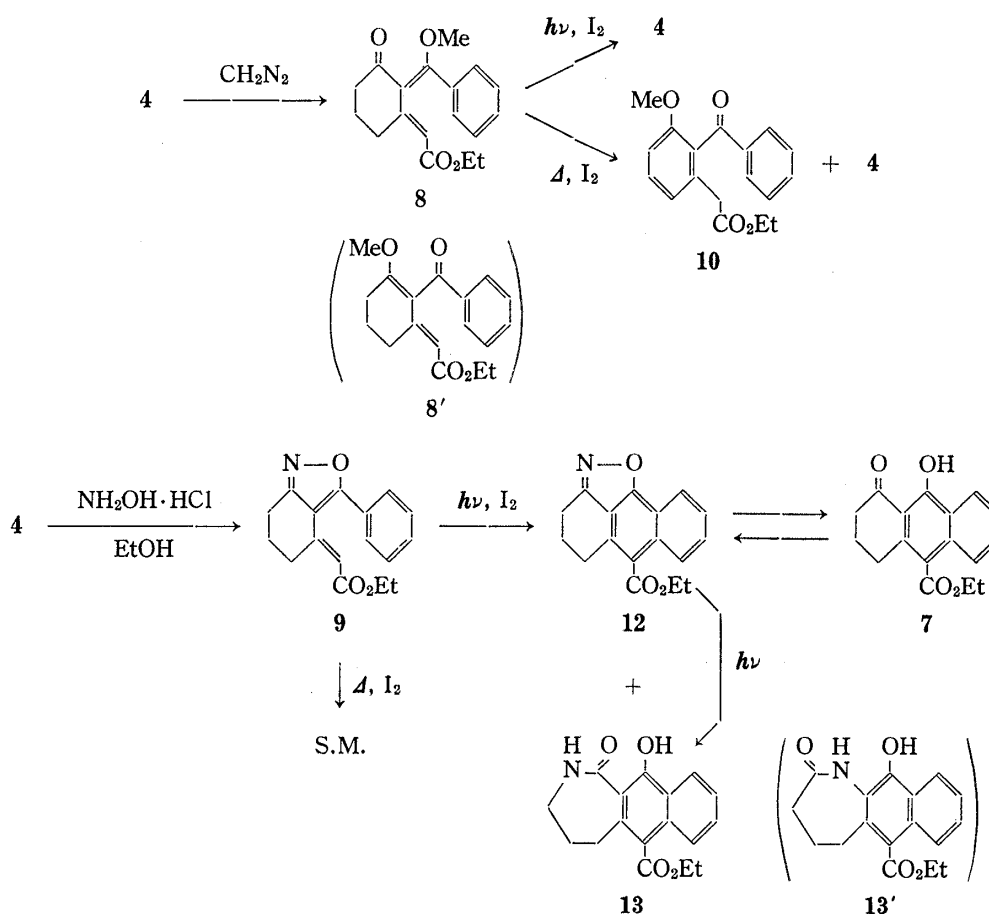


Chart 4

ring-closure of **9** did not occur either in the presence or absence of oxidizing agent, photochemical ring-closure occurred on irradiation of a benzene solution of **9** in the presence of an oxidizing agent such as iodine or selenium dioxide, giving **12** and **13**. The reaction was monitored by TLC and it was found that the initial photoproduct **12** was gradually converted into **13**; this was confirmed by photoirradiation of the isolated **12**. The structure of the product (**12**) was assigned from spectral and analytical data and also the following chemical transformations: deprotection of the isoxazole ring of **12** by treatment with hydrochloric acid in acetone gave a high yield of **7**, which was identical with an authentic sample obtained from **4**, and oximation of **7** followed by cyclization with ethyl chloroformate in pyridine gave the ordinal isoxazole **12**. The structure of the photo-Beckmann product (**13**) was assigned from the spectral and analytical data, mainly from a consideration of the nuclear magnetic resonance ($^1\text{H-NMR}$) spectra. The isomeric structure (**13'**) was readily ruled out by a deuterium labelling experiment: deuterium labelling of the NH proton at δ 6.5 resulted in the reduction of the quartet signal at δ 3.22 (methylene protons ascribed to CH_2NHCO or CH_2CONH) to a triplet. Therefore, the signal at δ 3.22 is assigned to the methylene protons adjacent to the NH group.⁸⁾

These photochemical and thermal properties of **9** together with those of **4** strongly support the view that cyclization of the trienes (**2**) to the anthracenones (**3**) occurs photochemically. This is the first successful pericyclic reaction of a fixed triene with the isoxazole ring.

Experimental

All melting and boiling points are uncorrected. The infrared (IR) absorption spectra were recorded on a Shimadzu IR-27G spectrometer, and NMR spectra on a Hitachi R-20A (60 MHz) or a Hitachi R-22 (90 MHz) spectrometer (with tetramethylsilane as an internal standard). The ultraviolet (UV) absorption spectra were recorded on a Hitachi 124 spectrometer. Low- and high-resolution mass spectra (MS) were obtained with Hitachi RMU-6D and JEOL JMS D-300 instruments, with a direct inlet system at 70 eV. Column chromatography was carried out on Merck Silica-gel 60.

Conversion of 2-Benzoyl-3-chlorocyclohex-2-enone into 2-Benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (4) and 3,8-Dioxo-1-phenyl-5,6,7,8-tetrahydro-3H-2-benzopyran (5)—A solution of ethyl *tert*-butyl malonate⁹⁾ (1.14 g, 6.04 mmol) in dry benzene (5 ml) was added dropwise to a stirred suspension of NaH (290 mg, 6.04 mmol) in dry benzene (10 ml) at room temperature. The mixture was stirred at room temperature for 15 min and a solution of 2-benzoyl-3-chlorocyclohex-2-enone³⁾ (709 mg, 3.02 mmol) in dry benzene (5 ml) was added in portions during a few minutes. After the reaction mixture had been heated at 60°C for 14 h, it was cooled to 0°C and quenched with water (30 ml). The separated aqueous layer was acidified with aqueous 10% hydrochloric acid and extracted with benzene (30 $\times$ 2 ml). The combined benzene layer was washed with brine, dried (MgSO_4), and concentrated to 15 ml. *p*-Toluenesulfonic acid (100 mg) was added to the benzene solution and the mixture was heated under reflux for 5 h. After cooling, the organic layer was washed with saturated aqueous NaHCO_3 and brine, dried (MgSO_4), and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (benzene: ethyl acetate = 9:1 as the eluting solvent) to give a 44% yield (380 mg) of **4** as a yellow oil, bp 170–190°C/0.7 mmHg (bath temperature). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1730, 1680, and 1660; NMR (10% solution in CDCl_3) δ : 1.13 (3H, t, J = 6.5 Hz, CH_3), 1.8–2.8 (6H, m, $\text{CH}_2 \times 3$), 3.19 (2H, s, CH_2), 4.03 (2H, q, J = 6.5 Hz, CH_2), and 7.3–7.95 (5H, m, ArH); UV $\lambda_{\text{max}}^{\text{ethanol}}$ nm: 245. Exact mass Calcd for $\text{C}_{17}\text{H}_{18}\text{O}_4$: 286.1204. Found: 286.1204.

Further elution with the same solvent gave a 4% yield (28 mg) of **5** as a solid. Recrystallization from benzene–pet. ether gave an analytical sample, mp 171–173.5°C. Anal. Calcd for $\text{C}_{15}\text{H}_{12}\text{O}_3$: C, 74.99; H, 5.03. Found: C, 74.69; H, 4.95. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1740 and 1685; NMR (10% solution in CDCl_3) δ : 1.9–3.0 (6H, m, $\text{CH}_2 \times 3$), 6.08 (1H, t, J = 1.5 Hz, =CH), and 7.45 (5H, s, ArH); MS m/e : 240 (M^+).

General Procedure for the Photocyclization of 2-Benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (4) under Various Conditions—A solution of **4** in degassed solvent was irradiated with a 350W high-pressure mercury lamp in a sealed quartz vessel. Removal of the solvent *in vacuo* followed by preparative TLC on silica gel (benzene: ethyl acetate = 9:1 as the developing solvent) gave 10-ethoxycarbonyl-9-hydroxy-3,4-dihydroanthracen-1(2H)-one (**7**) as a solid together with the starting enone (**4**). Recrystallization of **7** from pet. ether–benzene gave an analytical sample, mp 79–80°C. Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_4$: C, 71.82; H, 5.67. Found: C, 71.67; H, 5.70. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1720 and 1620; NMR (10% solution in CDCl_3) δ : 1.46 (3H, t, J = 7 Hz, CH_3), 2.0–3.3 (6H, m, $\text{CH}_2 \times 3$), 4.51 (2H, q, J = 7 Hz, CH_2), 7.3–7.9 (3H, m, ArH), 8.3–8.55 (1H, m, ArH), and 14.49 (1H, s, OH); MS m/e : 284 (M^+). The reaction conditions and yields of the products (**7** and **4**) are listed in Table I.

3-Ethoxycarbonylmethylene-2-(1-methoxy-1-phenylmethylene)cyclohexanone (8)—A large excess of diazomethane in ether was added to an ether solution of 2-benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (320 mg, 1.12 mmol) and the solution was allowed to stand at room temperature for 12 h. Removal of the solvent by evaporation *in vacuo* gave a residue, which was purified by column chromatography on silica gel (benzene: ethyl acetate=9:1 as the eluting solvent) to give a 25% yield (83 mg) of **8** as a solid. Recrystallization from *n*-hexane gave a pure sample, mp 112–114°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1690 and 1665; NMR (10% solution in CDCl₃) δ : 1.16 (3H, t, *J*=7 Hz, CH₃), 1.7–3.3 (6H, m, CH₂×3), 3.52 (3H, s, OCH₃), 4.03 (2H, q, *J*=7 Hz, CH₂), 5.15 (1H, m, =CH), and 7.1–8.0 (5H, m, ArH); UV $\lambda_{\text{max}}^{\text{ethanol}}$ nm: 246 and 290. Exact mass Calcd for C₁₈H₂₀O₄: 300.1362. Found: 300.1364.

Photoreaction of 8—A solution of **8** (71 mg, 0.24 mmol) and iodine (15 mg, 0.06 mmol) in degassed benzene (25 ml) was irradiated with a 350W high-pressure mercury lamp in a quartz vessel at 15°C for 7.5 h. Work-up as described in the general procedure for the photoreaction of **4** gave a 55% yield (37 mg) of the demethylated material (**4**), which was identical with an authentic specimen.

Thermolysis of 8—A mixture of **8** (70 mg, 0.24 mmol) and iodine (15 mg, 0.06 mmol) in dry benzene (4 ml) was heated under reflux for 12 h. The reaction mixture was washed with sat. aqueous Na₂S₂O₃ and brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (benzene: ethyl acetate=9:1 as the developing solvent) to give a 22% yield (15 mg) of 2-ethoxycarbonylmethyl-6-methoxybenzophenone (**10**) as a pale yellow oil and a 34% yield (23 mg) of the demethylated material (**4**). **10**: bp 160–180°C/5 mmHg (bath temperature). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1725 and 1665; NMR (10% solution in CDCl₃) δ : 1.02 (3H, t, *J*=7 Hz, CH₃), 3.53 (2H, s, CH₂), 3.64 (3H, s, OCH₃), 3.92 (2H, q, *J*=7 Hz, CH₂), 6.89 (1H, d, *J*=7 Hz, ArH), 7.10 (1H, d, *J*=7 Hz, ArH), 7.3–7.55 (4H, m, ArH), and 7.7–7.9 (2H, m, ArH). Exact mass Calcd for C₁₈H₁₈O₄: 298.1205. Found: 298.1208.

The compound (**4**) was identical with an authentic specimen.

Isoxazole Formation of 2-Benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone (4)—A solution of **4** (177 mg, 0.17 mmol) and hydroxylamine·hydrochloride (50 mg, 0.2 mmol) in ethanol (1 ml) was heated under reflux for 2 h. After removal of the solvent *in vacuo*, the residue was partitioned between water (10 ml) and chloroform (30 ml). The organic layer was washed with sat. aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (*n*-hexane: ethyl acetate=4:1 as the developing solvent) to give a 48% yield (85 mg) of 4-ethoxycarbonylmethylidene-3-phenyl-4,5,6,7-tetrahydro[2,1]benzisoxazole (**9**) and a 26% yield (45 mg) of 4-ethoxycarbonylmethyl-3-phenyl-6,7-dihydro[2,1]benzisoxazole (**11**). **9**: An analytical sample was obtained by recrystallization from *n*-hexane, mp 95.5–96.5°C. Anal. Calcd for C₁₇H₁₇NO₃: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.05; N, 5.01. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1700, 1635, and 1620; NMR (10% solution in CDCl₃) δ : 1.23 (3H, t, *J*=7 Hz, CH₃), 1.8–2.2 (2H, m, CH₂), 2.8–3.4 (4H, m, CH₂×2), 4.12 (2H, q, *J*=7 Hz, CH₂), 6.15 (1H, s, =CH), and 7.3–7.6 (5H, m, ArH); UV $\lambda_{\text{max}}^{\text{ethanol}}$ nm: 233 and 265; MS *m/e*: 283 (M⁺). **11**: A pure sample was obtained by distillation under reduced pressure, bp 215–220°C/5 mmHg (bath temperature). IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1730, 1640, and 1590. NMR (10% solution in CDCl₃) δ : 1.07 (3H, t, *J*=7 Hz, CH₃), 2.4–3.0 (4H, m, CH₂×2), 3.21 (2H, s, CH₂), 3.92 (2H, q, *J*=7 Hz, CH₂), 5.82 (1H, t, *J*=4 Hz, =CH), and 7.48 (5H, s, ArH); UV $\lambda_{\text{max}}^{\text{ethanol}}$ nm: 252. Exact mass Calcd for C₁₇H₁₇NO₃: 283.1208. Found: 283.1208.

Photoreaction of 9 to 12 and 13—i) A solution of **9** (87 mg, 0.31 mmol) and iodine (15 mg, 0.06 mmol) in degassed benzene (25 ml) was irradiated with a 350 W high-pressure mercury lamp in a quartz vessel at 15°C for 5.5 h. The reaction mixture was washed with sat. aqueous Na₂S₂O₃ and brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was subjected to preparative TLC on silica gel (*n*-hexane: ethyl acetate=2:1 as the developing solvent) to give a 20% yield (18 mg) of the cyclized isoxazole (**12**) and an 11% yield (11 mg) of the lactam (**13**). **12**: A pure sample was obtained by recrystallization from *n*-hexane, mp 66–68°C. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 1700, 1650, 1610, and 1580; NMR (10% solution in CDCl₃) δ : 1.47 (3H, t, *J*=7 Hz, CH₃), 2.1–2.4 (2H, m, CH₂), 3.0–3.3 (4H, m, CH₂×2), 4.54 (2H, q, *J*=7 Hz, CH₂), 7.3–7.8 (3H, m, ArH), and 8.2–8.5 (1H, m, ArH). Exact mass Calcd for C₁₇H₁₅NO₃: 281.1049. Found: 281.1049. **13**: An analytical sample was obtained by recrystallization from *n*-hexane, mp 196–198°C. Anal. Calcd for C₁₇H₁₇NO₄: C, 68.21; H, 5.23; N, 4.68. Found: C, 67.99; H, 5.69; N, 4.82. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3400, 1700, 1620 and 1460; NMR (10% solution in CDCl₃) δ : 1.43 (3H, t, *J*=7.5 Hz, CH₃), 2.18 (2H, q, *J*=7 Hz, CH₂), 2.92 (2H, t, *J*=7 Hz, CH₂), 3.22 (2H, q, *J*=7 Hz, CH₂NH), 4.44 (2H, q, *J*=7.5 Hz, CH₂), 6.5 (1H, bs, NH), 7.4–7.8 (3H, m, ArH), 8.3–8.5 (1H, m, ArH) and 11.88 (1H, s, OH); UV $\lambda_{\text{max}}^{\text{ethanol}}$ nm: 225 and 253; MS *m/e*: 299 (M⁺).

ii) A solution of **9** (94 mg, 0.33 mmol) and iodine (20 mg, 0.08 mmol) in degassed benzene (35 ml) was irradiated at 15°C for 22 h. Work-up as described above gave **12** and **13** in 11% (10 mg) and 56% yields (56 mg), respectively.

iii) A solution of **9** (15 mg, 0.05 mmol) and SeO₂ (7 mg, 0.06 mmol) in degassed benzene was irradiated at 15°C for 7 h. Work-up as described above gave **12** and **13** in 41% (6 mg) and 26% yields (4 mg), respectively.

Photoreaction of 12 into 13—i) A solution of **12** (9 mg, 0.03 mmol) in degassed benzene (5 ml) was irradiated with a 350 W high-pressure mercury lamp in a quartz vessel at 15°C for 10 h. The solvent was removed *in vacuo* to give a residue, which was subjected to column chromatography on silica gel (*n*-hexane:

ethyl acetate=2:1 as the eluting solvent) to give a 60% yield (5.7 mg) of 13, which was identical with an authentic specimen.

ii) A solution of 12 (9 mg, 0.03 mmol) and two drops of hydrogen iodide in degassed benzene (5 ml) was irradiated at 15°C for 2.5 h. Water (2 ml) was added to the mixture, and the organic layer was washed with brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified as described above to give a 40% yield (4 mg) of 13.

Alternative Synthesis of 12 from 7—A solution of the anthracenone (7) (171 mg, 0.06 mmol) and hydroxylamine·hydrochloride (84 mg, 1.2 mmol) in ethanol (5 ml) was heated under reflux for 20 h. After removal of the solvent *in vacuo* the residue was partitioned between water (10 ml) and chloroform (10 ml). The aqueous layer was extracted with chloroform (10 ml × 2). The combined organic layer was washed with sat. aqueous NaHCO₃ and brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (*n*-hexane: ethyl acetate: benzene=5:3:2 as the eluting solvent) to give a 32% yield (67 mg) of the oxime of 7 as a solid, which was used for the next reaction without further purification. IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm⁻¹: 3600, 1700, and 1640; NMR (10% solution in CDCl₃) δ : 1.44 (3H, t, *J*=6 Hz, CH₃), 1.7–2.0 (2H, m, CH₂), 2.8–3.1 (4H, m, CH₂ × 2), 4.49 (2H, q, *J*=6 Hz, CH₂), 7.3–7.9 (3H, m, ArH), 8.04 (1H, s, OH), 8.2–8.5 (1H, m, ArH), and 12.87 (1H, s, OH). Exact mass calcd for C₁₇H₁₇NO₄: 299.1158. Found: 299.1169.

Ethyl chloroformate (34 mg, 0.31 mmol) was added dropwise to a solution of the oxime (67 mg, 0.22 mmol) and pyridine (25 mg, 0.32 mmol) in chloroform (5 ml) at room temperature and the mixture was stirred for 1 h. Water (2 ml) was added to the reaction mixture, and the organic layer was washed with brine, dried (MgSO₄), and concentrated *in vacuo* to give the oxime O-ethoxycarbonate. A suspension of this product with silica gel (600 mg) in benzene (6 ml) was stirred at room temperature for 1 d. After removal of the silica gel by filtration under reduced pressure, the solution was concentrated *in vacuo* to give a 76% yield (48 mg) of 12, which was identical with an authentic specimen.

Acid Hydrolysis of 12 to 7—A solution of 12 (39 mg, 0.11 mmol) in 5% hydrochloric acid in acetone (1 ml) was heated under reflux for 2.5 h. The solvent was removed *in vacuo* to give a residue, which was partitioned between water (3 ml) and methylene chloride (10 ml). The organic layer was washed with brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (benzene: ethyl acetate=9:1 as the eluting solvent) to give an 83% yield (33 mg) of 7, which was identical with an authentic specimen.

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