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

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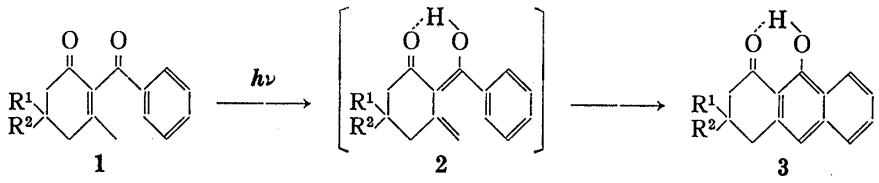
Preparation and cyclization of 2-benzoyl-3-ethoxycarbonylmethylcyclohex-2-enone and its derivatives have been investigated. Photochemical ring-closure followed by oxidative dehydrogenation was observed in suitably fixed triene derivatives. The results suggest that the cyclization of the photoenols (trienes) 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 reported[1] 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 reported[3] the related photocyclization of 2-aroyl-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-aroylcyclohex-2-enone derivatives and propose here that the cyclization of the trienes (**2**) to the anthracenones (**3**) occurs photochemically.



1 **2** **3**

Chart 1

Results and Discussion

To obtain a more stable enol (triene) intermediates than the enol (**2**) derived from the 2-aroyl-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*-toluenesulfonic 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-aroyl-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

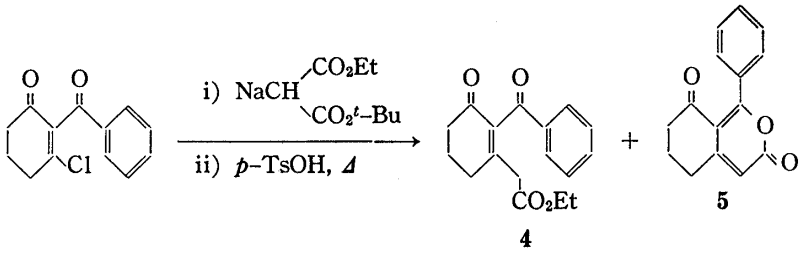


Chart 2

was found to favor the photocyclization. The results using the Lewis acid are consistent with the assumption[3] 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 anthracenone (**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.

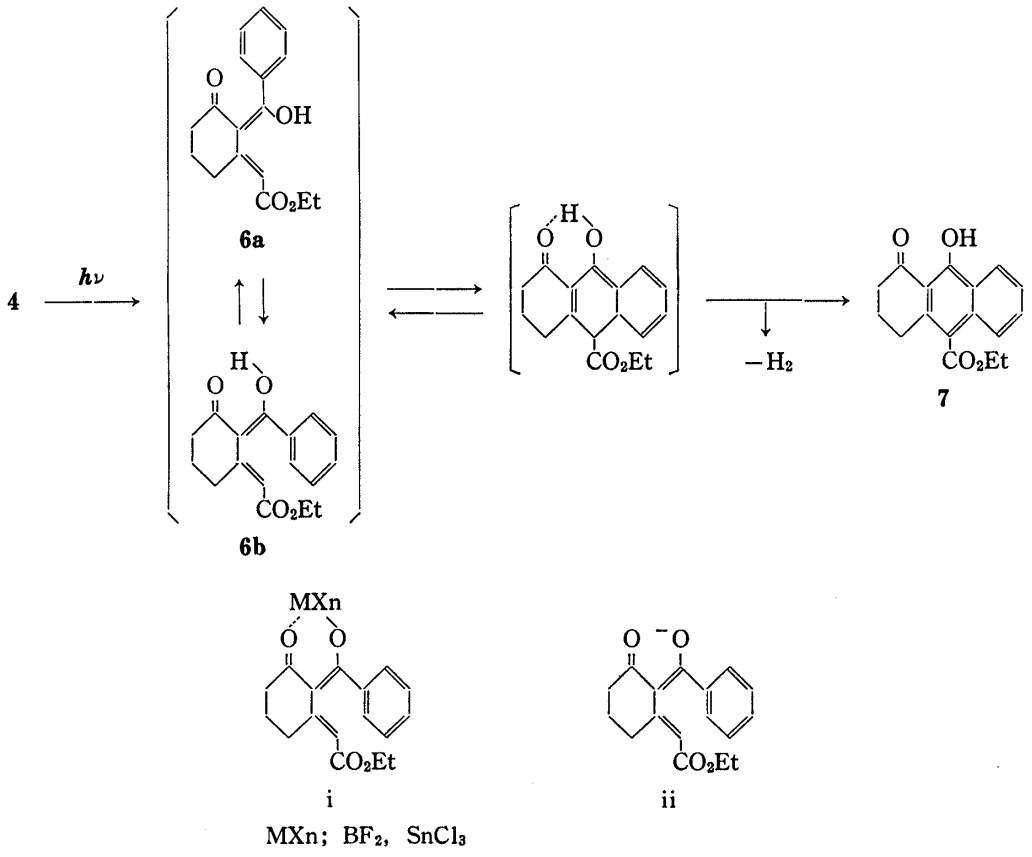


Chart 3

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 demethylation[5] of **8** into **4** and thermal aromatization[6] 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 ethanol[7] 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**)	Yields[a] (%) S.M. (**4**)
1	in Et_2O, 15°C, 40 h, $h\nu$[b]	18	39
2	in Et_2O, BF_3–Et_2O, 15°C, 20 h, $h\nu$[b]	28	39
3	in Et_2O–EtOH, $SnCl_4$, 15°C, 70 h, $h\nu$[b]	33	29
4	in Et_2O, Et_3N, 15°C, 20 h, $h\nu$[b]	19	23
5	in EtOH, EtONa, 15°C, 50 h, $h\nu$[b]	42	Trace
6	in Et_2O, I_2, 15°C, 20 h, $h\nu$[b]	14	28
7	in $C_6H_5NO_2$, 20 h, reflux	Complex mixture[c]	
8	in $C_6H_5NO_2$, $AlCl_3$, 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.

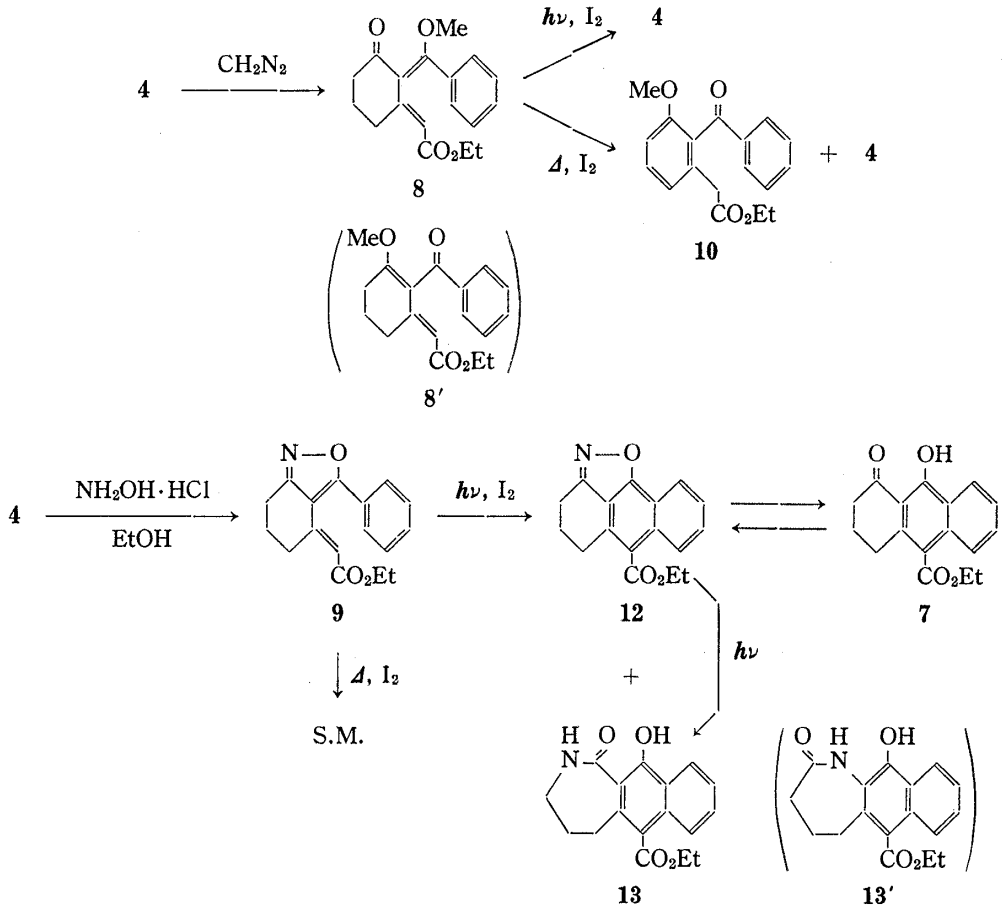


Chart 4

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}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 malonate[9] (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-enone[3] (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 (30×2 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 $\nu_{max}^{CHCl_3}$ 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, $CH_2\times3$), 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 $\lambda_{max}^{ethanol}$ nm: 245. Exact mass Calcd for $C_{17}H_{18}O_4$: 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 $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.69; H, 4.95. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 and 1685; NMR (10% solution in $CDCl_3$) δ: 1.9—3.0 (6H, m, $CH_2\times3$), 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 $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.67; H, 5.70. IR $\nu_{max}^{CHCl_3}$ 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, $CH_2\times3$), 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 and 1665; NMR (10% solution in $CDCl_3$) δ: 1.16 (3H, t, J=7 Hz, CH_3), 1.7—3.3 (6H, m, $CH_2\times3$), 3.52 (3H, s, OCH_3), 4.03 (2H, q, J=7 Hz, CH_2), 5.15 (1H, m, =CH), and 7.1—8.0 (5H, m, ArH); UV $\lambda_{max}^{ethanol}$ nm: 246 and 290. Exact mass Calcd for $C_{18}H_{20}O_4$: 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 $Na_2S_2O_3$ and brine, dried ($MgSO_4$), 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 and 1665; NMR (10% solution in $CDCl_3$) δ: 1.02 (3H, t, J=7 Hz, CH_3), 3.53 (2H, s, CH_2), 3.64 (3H, s, OCH_3), 3.92 (2H, q, J=7 Hz, CH_2), 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 $C_{18}H_{18}O_4$: 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 $NaHCO_3$ and brine, dried ($MgSO_4$), 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 $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.84; H, 6.05; N, 5.01. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1635, and 1620; NMR (10% solution in $CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, CH_3), 1.8—2.2 (2H, m, CH_2), 2.8—3.4 (4H, m, $CH_2\times2$), 4.12 (2H, q, J=7 Hz, CH_2), 6.15 (1H, s, =CH), and 7.3—7.6 (5H, m, ArH); UV $\lambda_{max}^{ethanol}$ 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1640, and 1590. NMR (10% solution in $CDCl_3$) δ: 1.07 (3H, t, J=7 Hz, CH_3), 2.4—3.0 (4H, m, $CH_2\times2$), 3.21 (2H, s, CH_2), 3.92 (2H, q, J=7 Hz, CH_2), 5.82 (1H, t, J=4 Hz, =CH), and 7.48 (5H, s, ArH); UV $\lambda_{max}^{ethanol}$ nm: 252. Exact mass Calcd for $C_{17}H_{17}NO_3$: 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 $Na_2S_2O_3$ and brine, dried ($MgSO_4$), 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1650, 1610, and 1580; NMR (10% solution in $CDCl_3$) δ: 1.47 (3H, t, J=7 Hz, CH_3), 2.1—2.4 (2H, m, CH_2), 3.0—3.3 (4H, m, $CH_2\times2$), 4.54 (2H, q, J=7 Hz, CH_2), 7.3—7.8 (3H, m, ArH), and 8.2—8.5 (1H, m, ArH). Exact mass Calcd for $C_{17}H_{15}NO_3$: 281.1049. Found: 281.1049. **13**: An analytical sample was obtained by recrystallization from *n*-hexane, mp 196—198°C. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.23; N, 4.68. Found: C, 67.99; H, 5.69; N, 4.82. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 1700, 1620 and 1460; NMR (10% solution in $CDCl_3$) δ: 1.43 (3H, t, J=7.5 Hz, CH_3), 2.18 (2H, q, J=7 Hz, CH_2), 2.92 (2H, t, J=7 Hz, CH_2), 3.22 (2H, q, J=7 Hz, CH_2NH), 4.44 (2H, q, J=7.5 Hz, CH_2), 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 $\lambda_{max}^{ethanol}$ 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 SeO_2 (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 ($MgSO_4$), 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 $NaHCO_3$ and brine, dried ($MgSO_4$), 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 $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 1700, and 1640; NMR (10% solution in $CDCl_3$) δ: 1.44 (3H, t, J=6 Hz, CH_3), 1.7—2.0 (2H, m, CH_2), 2.8—3.1 (4H, m, $CH_2\times2$), 4.49 (2H, q, J=6 Hz, CH_2), 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 $C_{17}H_{17}NO_4$: 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 ($MgSO_4$), 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 ($MgSO_4$), 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.

References and Notes

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