Photocycloaddition of Coumarin to Tetramethylethylene. A Photoreaction Associated with the Apparent Interception of the Coumarin Singlet Excimer[1,2]

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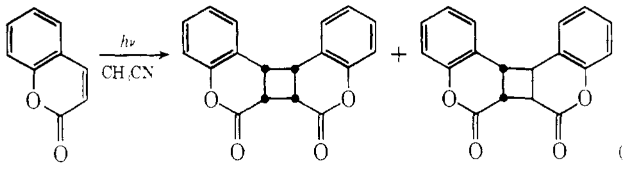
Abstract: Photolysis of 0.3 *M* solutions of coumarin in the presence of 3.0 *M* tetramethylethylene (TME) leads to the known cyclobutane adduct, III (4,4,5,5-tetramethyl-3,6-dihydrocyclobuta[*c*]-2-coumarin), with a quantum efficiency of ~3 × 10^{-3}. Quenching studies indicate that the reaction proceeds *via* coumarin singlet and triplet excited states. Despite the inefficiency of this reaction, TME completely quenches coumarin singlet and triplet photodimerization. Evidence presently available indicates the coumarin monomeric singlet species to be very short lived (~10^{-12} sec) and its complete interception by TME would require a rate constant in excess of the diffusion-controlled value. It has previously been suggested that coumarin singlets dimerize *via* an excimer, and the present observations are interpreted as the interception of this excimer, perhaps *via* an excimer–exciplex exchange reaction.

Coumarin has historically been the subject of intense photochemical[3,4] and spectroscopic[4,5] interest, in great part as a consequence of its importance in biological systems.[4] Its photochemistry has been particularly fascinating because of the marked sensitivity of its photodimerization (eq 1) to solvent polarity[6] and halocarbon solvents.[3] The former effect has been attributed to preferential dimerization of coumarin excimers ($^1CC^*$) in polar media, and the latter phenomenon was interpreted as a "heavy-atom" effect on the probability of closure of an intermediate diradical ($^3C_2^*$) to give IIb.[3] The complete mechanism suggested[3] is outlined in Scheme I. It should be noted that nonradiative decay of the excited singlet state accounts for better than 99% of the absorbed photons.



(1)

I IIa IIb

Scheme I

$$C \xrightarrow{h\nu} {}^1C^* \quad (2)$$

$${}^1C^* \xrightarrow{k_d} C \quad (3)$$

$${}^1C^* \xrightarrow{k_{isc}} {}^3C^* \quad (4)$$

$${}^1C^* + C \xrightarrow{k_{ex}} {}^1CC^* \quad (5)$$

$${}^1CC^* \longrightarrow \text{IIa} \quad (6)$$

$${}^1CC^* \longrightarrow 2C \quad (7)$$

$${}^3C^* \longrightarrow C \quad (8)$$

$${}^3C^* + C \longrightarrow 3C_2^* \quad (9)$$

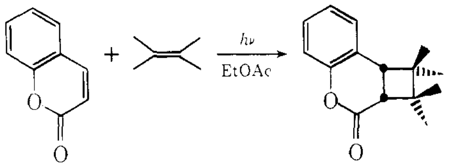
$$3C_2^* \longrightarrow \text{IIb} \quad (10)$$

$$3C_2^* \longrightarrow 2C \quad (11)$$

In addition to dimerizing, the coumarin excited state has also been made to add to olefins.[7,8] This reaction is particularly relevant to skin photosensitization by coumarin derivatives, where cycloaddition with the pyrimidine bases of DNA may be involved.[5c,9] Our attention was drawn to coumarin–olefin photocycloaddition by the report[8] that triplet sensitization was necessary for the reaction. This seemed to contrast with the ability of coumarin to dimerize *via* the singlet state, albeit only in polar solvents, and could be interpreted as a manifestation of the proposed requirement for an excimer precursor to the dimer. We thus decided to study the mechanistic details of the cycloaddition.[10]

Results

A. Coumarin Photocycloaddition to Tetramethylethylene (TME). An ethyl acetate solution of coumarin (0.3 *M*) and TME (3.0 *M*) was irradiated for 68 hr using a 450-W medium pressure mercury lamp and a soft glass filter (λ >310 nm). Vapor phase chromatographic (vpc) analysis indicated a 4% conversion to a product, which was isolated and identified as the known[8] 4,4,5,5-tetramethyl-3,6-dihydrocyclobuta[*c*]-2-coumarin (III), the expected cycloadduct[8,11] (eq 12). None of the normally observed coumarin dimer (IIb) could be detected; when the irradiation was done in acetonitrile, the cycloadduct could again be isolated but neither IIa nor IIb were formed.



(12)

III

B. Quantum Efficiencies for Formation of III. Quantum efficiencies were determined at 313 nm in several solvents, using coumarin photodimerization as a secondary actinometer. At 3.0 *M* TME, values observed are (1) $\phi_{III}(CCl_4)$ = 4.4 × 10^{-3}, (2) ϕ_{III}(EtOAc) = 3.0 × 10^{-3}, (3) $\phi_{III}(CH_3CN)$ = 3.4 × 10^{-3}.

C. Quenching of III by *cis*-Piperylene. Quenching of the cycloaddition by *cis*-piperylene is observed,[12] but it is incomplete! The quenching data, presented in the usual Stern–Volmer fashion, are given in Table I. Limiting quenching appears in each of the solvents at *ca.* 0.2 *M* piperylene. The limiting quenching observed (using repetitive measurements at 0.2 *M* diene) is (1) CCl_4, 23 ± 3%; (2) EtOAc, 37 ± 6%; (3) CH_3CN, 30 ± 4%. These data permit the quenching efficiencies (ϕ_{III}) to be dissected into singlet ($^1\phi_{III}$) and triplet ($^3\phi_{III}$) components as in Table II.

D. Photocycloaddition as a Function of TME Concentration. The overall quantum efficiency of cycloaddition decreases with decreasing TME concentration. Singlet and triplet efficiencies were determined at each point using 0.20

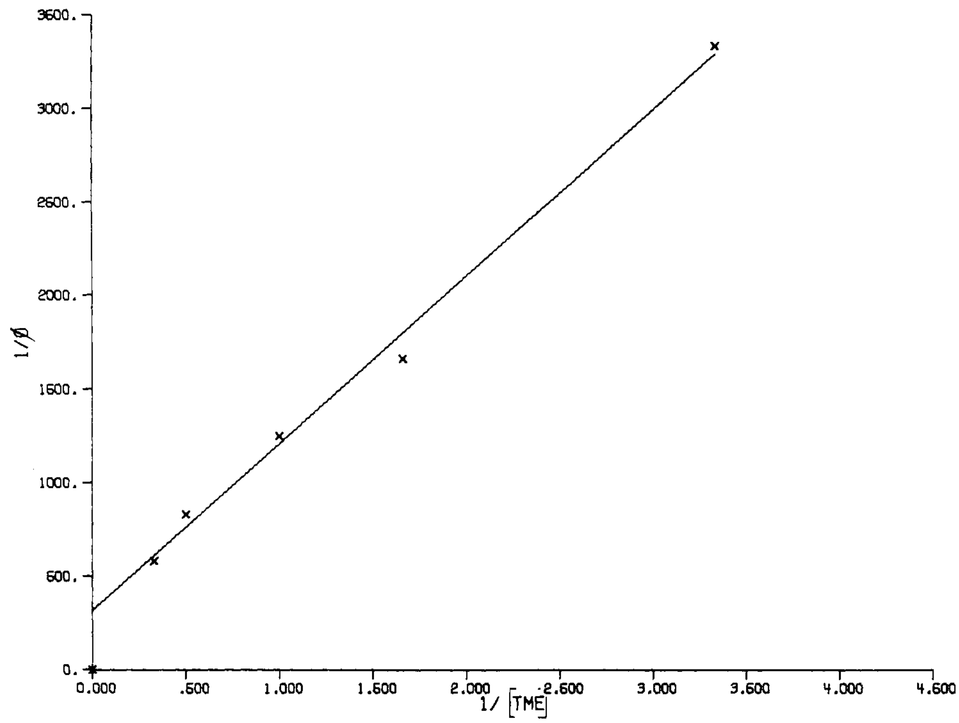


Figure 1. Plot of ${}^1\phi_{III}{}^{-1}$ *vs.* $[TME]^{-1}$ for formation of III in acetonitrile.

Table I. Quenching of Cycloaddition by *cis*-Piperylene in Several Solvents[a]

CCl_4		EtOAc		CH_3CN	
[Q], *M*	ϕ_0/ϕ	[Q], *M*	ϕ_0/ϕ	[Q], *M*	ϕ_0/ϕ
0.10	1.03	0.08	1.22	0.10	1.19
0.10	1.04	0.09	1.23	0.10	1.20
0.10	1.13	0.10	1.36	0.13	1.19
0.13	1.02	0.11	1.38	0.13	1.21
0.16	1.12	0.12	1.41	0.16	1.34
0.20	1.27	0.13	1.35	0.16	1.29
0.20	1.36	0.14	1.39	0.20	1.40
0.25	1.28	0.15	1.53	0.20	1.39
0.40	1.32	0.16	1.52	0.25	1.40
0.80	1.35	0.20	1.72	0.25	1.40
		0.25	1.75		

[a] All solutions 0.30 *M* in coumarin and 3.0 *M* in TME.

Table II. Quantum Efficiencies for Coumarin Singlet and Triplet Cycloaddition to TME upon Direct Irradiation[a]

Solvent	${}^1\phi_{III} \times 10^3$	${}^3\phi_{III} \times 10^3$
CCl_4	3.4	1.0
EtOAc	1.9	1.1
CH_3CN	2.4	1.0

[a] All solutions 0.30 *M* in coumarin and 3.0 *M* in TME.

Table III. Quantum Efficiencies for Singlet and Triplet Cycloaddition as a Function of TME Concentration in Acetonitrile[a]

[TME], *M*	${}^1\phi_{III} \times 10^4$	${}^3\phi_{III} \times 10^4$
3.0	24	10
2.0	18	9
1.0	11	12
0.60	9	11
0.30	4	8
0.10	2	15
0.05	1	14
0.01	1	3

[a] All solutions are 0.30 *M* in coumarin.

Table IV. Quantum Efficiencies for Sensitized Formation of III and the Benzophenone–TME Oxetane[a]

Solvent	${}^3\phi_{III}$ (sens)	ϕ_{ox}
CCl_4	0.104	0.022
EtOAc	0.073	0.019
CH_3CN	0.073	0.020

[a] All solutions 0.30 *M* in coumarin, 3.0 *M* in TME, and 0.037 *M* in benzophenone.

M piperylene and the data are shown in Table III. The ${}^1\phi_{III}$ values are plotted as $1/\phi$ *vs.* 1/TME in Figure 1. The points from 0.30 to 3.0 *M* TME show good linearity, with the least-squares derived slope = 892 ± 39 M^{-1} and the intercept = 312 ± 69. At the lower concentrations ($\leq$0.10 *M*) the reaction becomes more complex because IIa and IIb can now be isolated from the reaction mixture.

E. Sensitized Photocycloaddition of Coumarin to TME. As previously reported,[8] sensitization with benzophenone leads to the cycloadduct, III, as well as to the benzophenone-TME oxetane, 1,1-diphenyl-3,3,4,4-tetramethyl-2-oxycyclobutane. None of the triplet-derived coumarin dimer (IIb) was detected! Quantum efficiencies for cycloaddition (${}^3\phi_{III}$(sens)) and oxetane formation (ϕ_{ox}) were determined in several solvents and are presented in Table IV.

Since both TME and coumarin are capable of intercepting the benzophenone triplet, their effect individually on the photoreduction of benzophenone by benzhydrol was measured. Using ethyl acetate solutions containing 0.055 *M* benzophenone and 0.056 *M* benzhydrol, and irradiating with Uranium Yellow glass filtered light, the quantum efficiency for reduction (ϕ_{red}) was measured with and without quencher. The value of 0.60 without quencher[13] was identically reduced by 0.31 *M* coumarin or 3.0 *M* TME to ϕ_{red} = 0.04. Thus, at these concentrations, the two substrates intercept the benzophenone triplet with equal efficiency.

Discussion

The data presented above demonstrate that coumarin does indeed undergo photocycloaddition to TME without the presence of a sensitizer. Although the quantum efficiencies are some 20-fold lower than with sensitization, they are comparable to those previously observed for coumarin photodimerization ($\phi_{IIa} = \phi_{IIb} = 4 \times 10^{-4}$ in CH_3CN).[3] Furthermore, a substantial portion (70–80%) of the unsensitized cycloaddition is unquenchable by piperylene, and may be attributed to the coumarin excited singlet state. (It is of interest that there is heavy singlet involvement in both polar and nonpolar solvents, whereas coumarin singlet *dimerization* requires a polar medium.) However, *the most striking observation is the complete quenching by TME of coumarin singlet dimerization* in acetonitrile, when the olefin is present at ≥ 0.3 *M*. This is especially so in the light of the inefficiency of the TME cycloaddition itself.[14]

That *this quenching cannot be merely the result of an interception of the monomeric coumarin excited singlet state* is made evident by a consideration of presently available lifetime data. Recent attempts to measure coumarin fluorescence at room temperature have been uniformly unsuccessful,[5a,d,e] and ϕ_f has been estimated[5e] to be $\leq 10^{-4}$. Integration of the absorption band leads to a calculated[5d] radiative lifetime (τ_0) of 1.3×10^{-8} sec, so that from $\phi_f = \tau/\tau_0$, we can estimate $\tau \leq 1.3 \times 10^{-12}$ sec. One empirical manifestation of this extremely short singlet lifetime is the report[5d] of an unsuccessful attempt to measure the lifetime of fluorescence at 77°K ($\phi_f = 9 \times 10^{-3}$), on an apparatus capable of resolving lifetimes ≥ 2 nsec. This is despite the fact that, at this temperature, the rate of the nonradiative decay mode has been greatly reduced from that at room temperature.[5a,d,e] It is obvious that the short singlet lifetime does not involve intersystem crossing ($\phi_{isc} \sim 10^{-2}$),[3] but rather, facile decay to the ground state.[15,19]

Keeping the short lifetime of $^1C^*$ in mind, it can readily be demonstrated that it is *not* this species which TME is intercepting in the course of quenching IIa formation. Thus, the mechanism described in Scheme I leads to the following expression for ϕ_{IIa} (eq 13).

$$\phi_{IIa} = \left(\frac{k_{ex}[C]}{k_{ex}[C] + k_d + k_{isc}}\right)\left(\frac{k_6}{k_6 + k_7}\right) \quad (13)$$

At 0.3 *M* coumarin, $\phi_{IIa} = 4.4 \times 10^{-4}$ and $k_d \sim 10^{12}$ sec^{-1} (see above); k_{ex} may be assumed[21] to be diffusion controlled (1.8×10^{10} M^{-1} sec^{-1}).[22] Setting the probability of excimer closure to IIa ($k_6/(k_6 + k_7)) = P_{df}$, eq 13 becomes

$$4.4 \times 10^{-4} = P_{df}(5.4 \times 10^9/10^{12}) \quad (14)$$

and, solving for P_{df},[23]

$$P_{df} = 0.081 \quad (15)$$

Now, were elimination of the dimer due to interception of $^1C^*$ by TME (presumably *via* a reaction such as (16), with $^1(C \cdot TME)^*$ a complex capable of nonradiative decay and product formation), the appropriately modified Scheme I would yield a new expression for ϕ_{IIa} (eq 17).

$$^1C^* + TME \xrightarrow{k_q} {}^1(C \cdot TME)^* \quad (16)$$

$$\phi_{IIa} = P_{df}\left(\frac{k_{ex}[C]}{k_{ex}[C] + k_{isc} + k_d + k_q[TME]}\right) \quad (17)$$

We estimate our analytical procedure would have detected a $\phi_{IIa} \geq 4 \times 10^{-5}$, and one can easily calculate the value of k_q necessary for 3.0 *M* TME to reduce ϕ_{IIa} to this extent.

$$4 \times 10^{-5} = 8.1 \times 10^{-2}\left(\frac{5.4 \times 10^9}{10^{12} + 3k_q}\right) \quad (18)$$

$$kq = 3.3 \times 10^{12}\ M^{-1}\ sec^{-1} \quad (19)$$

The requisite value for k_q, being 200-fold larger than the diffusion-controlled rate constant, is physically impossible; *the interception of coumarin monomer cannot be the source of the observed quenching.*[25] *An alternative intermediate of longer lifetime is necessary, and we propose that this is the coumarin excimer.*[26] The suggested reaction is shown in eq 20 (note that though excimer interception is depicted as leading directly to cycloadduct, an intermediate exciplex is also feasible; see discussion below).

$$^1CC^* + TME \xrightarrow{k_r} III + C \quad (20)$$

Addition of eq 20 to Scheme I leads to an expression for the quantum efficiency of formation of III from the singlet state ($^1\phi_{III}$) as a function of [TME] (eq 21).

$$\frac{1}{^1\phi_{III}} = \frac{1}{\phi_{ex}} + \frac{1}{\phi_{ex}k_r\tau_{ex}[TME]} \quad (21)$$

In eq 21, $\phi_{ex} = k_{ex}[C]/(k_{ex}[C] + k_d + k_{isc})$ and $\tau_{ex} = 1/(k_6 + k_7)$. The dependence of $^1\phi_{III}$ on [TME] has been determined (Table III) and the data from 0.3 to 3.0 *M* TME yield the expected linear relationship (Figure 1). The large deviation of the intercept (312) from unity confirms the involvement of at least one energy wastage step prior to formation of III. If the reaction to give III involves no intermediate, as in eq 20, the intercept provides a value for ϕ_{ex} of *ca.* 3.2×10^{-3}, a number in surprisingly good agreement with the value of 5.4×10^{-3} one would estimate (*cf.* eq 14). From the slope plus the intercept, $k_r\tau_{ex} = 0.350$, and if one assumes k_r is diffusion controlled, the *lower limit* of τ_{ex} is 1.9×10^{-11} sec. Since $P_{df} = k_6/(k_6 + k_7)$ was previously calculated as 0.081 (eq 14), $k_7 = 11.3k_6$. Thus, $k_6 = 4.3 \times 10^9$ sec^{-1} and $k_7 = 4.9 \times 10^{10}$ sec^{-1} (these numbers will of course be correspondingly smaller if k_r is less than diffusion controlled).

Although the concept of a modestly long-lived excimer acting as a reagent seems reasonable, there have been surprisingly few reports of excimer (or exciplex) involvement in bimolecular photoreactions. One from the older literature invokes eq 22 to rationalize an increase in anthracene formation at high anthracene concentrations.[29] More recently, several groups[30] have observed a diene-induced enhancement of anthracene dimerization concomitant with the diene's quenching of anthracene fluorescence and proposed an interception of the exciplex, $^1AD^*$ (eq 23 and 24). The enhancement is sufficient to allow photodimerization of 9-phenylanthracene in the presence of piperylene,[30,31] whereas the substrate is normally photostable.[32] Still another example is the protonation by solvent of a naphthalene–acrylonitrile exciplex.[33] Though the reaction we are suggesting, as well as those cited above, involves simultaneous quenching and product formation, such does not necessarily have to be the case, as was recently demonstrated for the quenching of exciplexes of 9-cyanophenanthrene and various styrene derivatives.[34]

$$^1AA^* + A \longrightarrow A_2 + {}^1A^* \quad (22)$$

$$^1A^* + D \longrightarrow {}^1AD^* \quad (23)$$

$$^1AD^* + A \longrightarrow A_2 + D \quad (24)$$

There remains the question of whether eq 20 is not better represented by the sequence 25–27, where $^1(C \cdot TME)^*$ is a coumarin–TME exciplex.

$$^1CC^* + TME \longrightarrow {}^1(C \cdot TME)^* + C \quad (25)$$

$$^1(C \cdot TME)^* \longrightarrow III \quad (26)$$

$$^1(C \cdot TME)^* \longrightarrow C + TME \quad (27)$$

The eventual closure of such an exciplex (eq 26), were it to be formed, has ample precedent in the literature.[35,36] However, we are unaware of any prior proposal of an excimer–exciplex exchange reaction (eq 25). In fact, though the data in hand by no means require the inclusion of such an exciplex, some preliminary observations are suggestive of this possibility. Thus, one might expect a dependence of eq 25 on ionization potential of the olefin, by analogy with other singlet quenching acts proceeding *via* exciplex formation.[37] Our initial data with two additional olefins are consistent with these expectations; *i.e.*, product formation *via* singlet cycloaddition to TME (IP 8.05 eV),[37c] ethyl vinyl ether (EVE) (IP 8.49 eV),[37h] and *trans*-2-heptene (TH) (IP *ca.* 9.1 eV),[38] 3.0 *M* in ethyl acetate, is in the ratio 1.0:0.077: 0.0068.[39,40] Likewise, the pattern of products produced by the triplet cycloaddition to EVE and TH are identical with those observed from the singlet,[2] an occurrence most easily rationalized by invoking a common (exciplex) intermediate. There is precedent for singlet and triplet exciplexes having such identical product stereoselectivity.[34,42] Were the triplet cycloaddition to proceed through an exciplex, one might expect a dependence on olefin ionization potential analogous to that reported above for the singlet,[43] and such appears to be the case; *i.e.*, for TME–EVE–TH in ethyl acetate, the ratio of reactivities is 1.0:0.21:0.015.[44]

As regards the triplet component of the coumarin–TME cycloaddition, several facts are noteworthy. First, that there is a quenchable (triplet) component at all, while singlet dimerization has been totally eliminated, provides confirmation that intersystem crossing and singlet dimerization involve different species (*i.e.*, monomer *vs.* excimer). Second, the dimer derived from the coumarin monomer triplet (IIb) is completely quenched by 0.3 to 3.0 *M* TME,[44] and there is no apparent dependence of $^3\phi_{\mathrm{III}}$ on TME concentration in that range (Table III). These observations are entirely consistent when one considers that at a concentration of 0.3 *M*, coumarin effectively intercepts all coumarin triplets (rate constant = $3.5 \times 10^8\ M^{-1}\ \mathrm{sec}^{-1}$ (ethyl acetate)).[3] Thus the complete elimination of IIb requires total capture of coumarin triplets by TME and $^3\phi_{\mathrm{III}}$ must necessarily be independent of TME concentration. The rate constant required for the ^{3}C* + TME reaction to pre-empt dimerization is estimated[2] to be about $6 \times 10^9\ M^{-1}\ \mathrm{sec}^{-1}$! This is close of diffusion controlled and again consistent with an initial complexation (see above).

One can use the ϕ_{isc} value previously obtained[3] for coumarin in acetonitrile (7×10^{-3}) and $^3\phi_{\mathrm{III}}$ (1×10^{-3}) to estimate that ~14% of the triplet intermediate(s) (exciplex and/or diradical) goes on to cycloadduct. This is the same estimate one obtains from the sensitized cycloaddition ($^3\phi_{\mathrm{III}}$(sens) = 0.07), after correction for equally efficient transfer from sensitizer to 3.0 *M* TME and 0.3 *M* coumarin. The value of 14% may be compared with the corresponding value for coumarin triplet dimerization of ~2%.

Conclusions

The data presented herein are most readily rationalized by a mechanism of coumarin cycloaddition to TME at high concentrations as detailed in Scheme II. The novel aspect of this scheme is the proposed interception of the coumarin excimer by TME (eq 32), perhaps *via* an excimer–exciplex exchange reaction (eq 33). The observations reported herein constitute strong supportive evidence for the proposed[3] intermediacy of a coumarin excimer as a precursor to the singlet derived photodimer.

Scheme II

$$\mathrm{C} \longrightarrow {}^1\mathrm{C}^* \tag{28}$$

$${}^1\mathrm{C}^* \longrightarrow \mathrm{C} \tag{29}$$

$${}^1\mathrm{C}^* \longrightarrow {}^3\mathrm{C}^* \tag{30}$$

$${}^1\mathrm{C}^* + \mathrm{C} \longrightarrow {}^1\mathrm{CC}^* \tag{31}$$

$${}^1\mathrm{CC}^* + \mathrm{TME} \longrightarrow \mathrm{III} + \mathrm{C} \tag{32}$$

or

$$\left\{\begin{array}{ll} {}^1\mathrm{CC}^* + \mathrm{TME} \longrightarrow {}^1(\mathrm{C}\cdot\mathrm{TME})^* + \mathrm{C} & (33) \\ {}^1(\mathrm{C}\cdot\mathrm{TME})^* \longrightarrow \mathrm{III} & (34) \\ {}^1(\mathrm{C}\cdot\mathrm{TME})^* \longrightarrow \mathrm{C} + \mathrm{TME} & (35) \end{array}\right.$$

$${}^3\mathrm{C}^* + \mathrm{TME} \longrightarrow {}^3(\mathrm{C}\cdot\mathrm{TME})^* \tag{36}$$

$${}^3(\mathrm{C}\cdot\mathrm{TME})^* \longrightarrow \mathrm{C} + \mathrm{TME} \tag{37}$$

$${}^3(\mathrm{C}\cdot\mathrm{TME})^* \longrightarrow \mathrm{III} \tag{38}$$

Experimental Section

Chemicals. Acetonitrile (Baker Analytical reagent grade) was dried over calcium hydride and distilled through a Todd still prior to use. Carbon tetrachloride (Baker spectral grade or Mallinckrodt analytical reagent grade) and ethyl acetate (Matheson Coleman and Bell anhydrous, 99.5%) were distilled following treatment with Fisher type 4A molecular sieve. Benzophenone and coumarin (both from Eastman) were used as received. Deoxybenzoin (Aldrich) was purified by sublimation. Ethyl vinyl ether was dried over Fisher type 4A molecular sieve and distilled. *trans*-2-Heptene, *cis*-piperylene, and tetramethylethylene were all from Chemical Samples Co. and were molecularly distilled before use.

Analyses. All gas–liquid partition chromatography (glpc) data were obtained using a Varian-Aerograph Model 90-P chromatograph and disk integrator for preparative work and a Varian-Aerograph Model 1200 flame ionization chromatograph and disk integrator for analytical work. In all experiments designed to study the cycloaddition (and oxetane formation) of coumarin and the olefins, analyses were performed on a 5 ft × ⅛ in. stainless steel column packed with 3% SE-30 on Chromosorb W (acid washed, DMCS treated, 60/80 mesh) and programmed from 100 to 140° at 2°/min. Deoxybenzoin was used as an internal standard and retention times (air flow 300 ml/min, hydrogen flow 30 ml/min, and nitrogen flow 30 ml/min) were: 4 min, coumarin; 8 min, benzophenone; 11 min, deoxybenzoin; 13 min, TME cycloadduct; and 17 min, TME oxetane. Analyses for the coumarin dimers were performed as previously described.[3]

Photochemical Apparatus. Most comparative runs were done using a rotating turntable holding 25-mm o.d. Pyrex or soft glass photolysis tubes. A Hanovia 450-W type L mercury arc lamp filtered through soft glass or Uranium Yellow glass or through a potassium chromate–potassium hydroxide solution (for the 313-nm line)[45] was used. A Rayonet Photochemical Reactor and associated turntable (3500-Å lamps, Southern New England Ultraviolet Co.) were used in some experiments. Light intensities were determined by secondary actinometery using coumarin photodimerization.[3] The Pyrex or soft glass tubes were filled with 10-ml aliquots from a standard solution of the solid reactants. This ensured a reproducible quantity of reactants in each tube. In experiments where the amounts of reactants varied, the reactants were weighed into each tube and then 10 ml of the appropriate solvent was added. A slow stream of argon was bubbled through each of the solutions using 2 mm o.d. glass tubing for 45–60 min; each was sealed with a rubber stopple immediately after the delivery tube was withdrawn. If necessary, the tubes were refilled to a premarked solvent level with degassed solvent. Volatile olefins or quenchers were also injected through the rubber stopple, weighing the syringe before and after delivery.

Preparation of III. A solution of 0.69 g of coumarin, 0.10 g of benzophenone, and 3.96 g of TME in ethyl acetate was irradiated with Uranium Yellow filtered light from a 450-W Hanovia lamp for 5.75 hr. From 1500 mg of residue, 100 mg of III and 35 mg of oxetane were separated on a 5 ft × 0.25 in. 20% SF-96 column at 190°. III melted at 80–81° (81°)[8] and the oxetane melted at 123–124° (123–125°).[46] III showed the following characteristics: nmr ($\mathrm{CDCl_3}$) δ 0.74 (s, 3 H), 0.98, (s, 3 H), 1.20 (s, 3 H), 1.26 (s, 3 H), 3.05, 3.35 (AB quartet, 2 H), and 7.10 (m, 4 H); ir (KBr) 3.37, 3.44, 5.74, 6.33, 6.80, 6.93, 8.10, 8.50, 9.10, 13.25 μ; molecular ion, *m/e* 230. The oxetane showed the following characteristics: nmr ($\mathrm{CDCl_3}$) δ 1.06 (s, 6 H), 1.23 (s, 6 H), and 7.35 (m, 10 H); ir

(KBr) 3.42, 3.48, 6.32, 6.94, 8.72, 9.96, 10.42, 11.00, 11.70, 13.14 μ.

Quantum Efficiencies for Formation of III. Direct Irradiation. The quantum efficiency of cycloadduct formation under direct irradiation conditions was determined at 313 nm. Pyrex photolysis tubes were irradiated with a 450 Watt mercury arc lamp equipped with a Vycor filter sleeve and the 313-nm filter solutions. All the incident light was absorbed by 0.30 *M* coumarin. In this experiment the coumarin IIb dimerization in CCl_4 was used as a secondary actinometer for the determination of the average light intensity. The values obtained were 1.555×10^{16} photons/sec and 1.585×10^{16} photons/sec for an average light intensity of 1.570×10^{16} photons/sec. After 164 hr and 10 min of irradiation, the following quantities of cycloadduct, III, had formed: carbon tetrachloride, 16 mg (1.4% conversion); ethyl acetate, 11 mg (1.0% conversion); and acetonitrile, 12 mg (1.1% conversion). The calculated quantum yields for cycloadduct formation are: carbon tetrachloride, 0.0044; ethyl acetate, 0.0030; and acetonitrile, 0.0034.

Quantum Efficiencies for Formation of III by Sensitization. Solutions 0.30 *M* in coumarin, 0.037 *M* in benzophenone, and 3.0 *M* in TME were irradiated in Pyrex photolysis tubes with Uranium Yellow filtered light from a 450-Watt mercury lamp. Under these conditions, the light absorbed is predominantly the 366-nm line, for which wavelength ϵ_{Ph_2CO} 50 and $\epsilon_{coumarin}$ 0.11. A secondary actinometer, the sensitized coumarin IIb dimerization in ethyl acetate, was used to determine the light intensity of the lamp. The values obtained were 1.638×10^{17} and 1.642×10^{17} photons/sec for an average value of 1.640×10^{17} photons/sec. After 5.75 hr of irradiation, the following quantities of III were found: carbon tetrachloride, 135 mg (12.6% conversion); ethyl acetate, 95 mg (8.8% conversion); and acetonitrile, 90 mg (8.4% conversion). The calculated quantum yields for cycloadduct formation are: carbon tetrachloride, 0.104 ± 0.001; ethyl acetate, 0.073 ± 0.001; and acetonitrile, 0.070 ± 0.002.

The following quantities of oxetane were found by glpc analysis: carbon tetrachloride, 32 mg (21.2% conversion); ethyl acetate, 28 mg (18.2% conversion); and acetonitrile, 30 mg (20.1% conversion). The calculated quantum yields for oxetane formation are: carbon tetrachloride 0.022 ± 0.002; ethyl acetate, 0.019 ± 0.001; and acetonitrile, 0.020 ± 0.001.

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References and Notes

(1) Organic Photochemistry, Part XXVIII. Part XXVII: W. Lippke, W. Ferree, Jr., and H. Morrison, *J. Amer. Chem. Soc.*, **96**, 2134 (1974).

(2) Abstracted from the Doctoral Thesis of Paula P. Wells, Purdue University, May 1973.

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(7) G. O. Schenck, J. Kuhls, and C. H. Krauch, *Justus Liebigs Ann. Chem.*, **693**, 20 (1966).

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(10) One objective of this research was to ascertain whether the heavy-atom effect on coumarin photodimerization[3] extended to other substrates. Our results[2] show no consistent pattern of halocarbon enhancement of the cycloaddition reported herein.

(11) A second photoproduct is detectable by vpc but was too labile to be isolable.

(12) All of the coumarin loss in these experiments is accountable as cycloadduct, III.

(13) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, **84**, 1368 (1962).

(14) Since coumarin singlet dimerization is so dependent on a polar medium, a trivial explanation for the quenching would be the change in solvent polarity caused by addition of the TME to the acetonitrile. To test this possibility, we used 3.0 *M* hexane as an alternant diluent; IIa was easily observed, though the change in solvent polarity did cause a 60% reduction in dimer yield. It should be noted that TME eliminates IIa formation even when its concentration is reduced tenfold.

(15) The analogy with the DNA base, thymine, and its derivatives is striking. These compounds are only very weakly fluorescent at room temperature ($\phi_f \sim 10^{-4}$), show minimal intersystem crossing ($\phi_{isc} \sim 10^{-2}$), and have singlet lifetimes estimated at *ca.* 10^{-12} sec.[16-18]

(16) R. Kleopfer and H. Morrison, *J. Amer. Chem. Soc.*, **94**, 255 (1972).

(17) W. Hauswirth and M. Daniels, *Chem. Phys. Lett.*, **10**, 140 (1971); M. Daniels and W. Hauswirth, *Science*, **171**, 675 (1971); W. Hauswirth and M. Daniels, *Photochem. Photobiol.*, **13**, 157 (1971).

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(19) The source of this rapid decay remains anomalous. Cole[20] has suggested reversible opening of the lactone ring, but no spectroscopic observations have been forthcoming which support this. Rapid, reversible twisting about the double bond, as in a simple cycloalkene, might be a reasonable alternative. Song[5d] has suggested that the broadness and short lifetime of coumarin absorption and fluorescence "are likely to be a consequence of the breakdown of the discrete Born-Oppenheimer state by a nearby $^1n,\pi^*$ state in a manner described by the theory of radiationless transitions." Similar explanations may be derived for the thymine system.[15]

(20) R. S. Cole, *Diss. Abstr. B*, **29**, 933 (1968).

(21) J. B. Birks, *Prog. React. Kinet.* **5**, 181 (1970).

(22) Using $k = 8RT/3000\eta\ M^{-1}\ sec^{-1}$, and $\eta = 3.6 \times 10^{-3}$ P at 25° (*cf.* "International Critical Tables," Vol. VII, McGraw-Hill, New York, N.Y., 1930, p 213).

(23) By comparison, P_{df} for dimethylthymine is reported[24] to be 0.19.

(24) R. Lisewski and K. L. Wierzchowski, *Mol. Photochem.*, **3**, 231 (1971).

(25) The above discussion assumes no prior association of coumarin and TME in their ground states. Examination of the reaction mixtures, by uv absorption spectroscopy, gave no evidence of complexation.

(26) Emission attributable to coumarin excimers has been observed at low temperature[3,5] but no lifetime data are available. No excimer emission has been detected at room temperature, but only 0.5% of excited monomers could form excimers in competition with the rapid monomer decay. Weak emission from so few species might easily be undetectable.[27] Lifetime data available for aromatic hydrocarbons show no uniform relationship between monomer and excimer lifetimes, faster as well as slower decay having been observed.[28]

(27) Alternatively, coumarin excimers may be forming directly from trace aggregates[3,17] as has been suggested in the case at low temperature.[5e] The inability to detect such aggregates by thermal osmometry[3] sets an upper limit of some 3%, which still makes the number of potential excimers minimal.

(28) See ref 21, Table 2, pp 200 and 201.

(29) M. Suzuki, *Bull. Chem. Soc. Jap.*, **22**, 172 (1949); **23**, 120 (1950).

(30) J. Saltiel and D. E. Townsend, *J. Amer. Chem. Soc.*, **95**, 6140 (1973).

(31) R. O. Campbell and R. S. H. Liu, *Chem. Commun.*, 1191 (1970).

(32) In fact, an enhancement of dimer formation by piperylene has been observed in the coumarin system itself (Doctoral Thesis of R. E. Hoffman, Purdue University, January 1970). A 25% increase in IIa formation occurs with small (0.01 to 0.03 *M*) concentrations of piperylene, but the increase disappears at 0.1 *M* diene. The latter observation is in contrast with that reported for anthracene[30] and is difficult to rationalize in view of the inability of diene to quench "normal" IIa formation. Related observations have been made on the IIa formed at low mono-olefin concentrations.[2]

(33) R. M. Bowman, T. R. Chamberlain, C.-W. Huang, and J. J. McCullough, *J. Amer. Chem. Soc.*, **96**, 692 (1974).

(34) R. A. Caldwell and L. Smith, *J. Amer. Chem. Soc.*, **96**, 2994 (1974).

(35) For leading references, see ref 34. For a specific example involving TME, see: J. Saltiel, J. T. D'Agostino, O. T. Chapman, and R. D. Lura, *J. Amer. Chem. Soc.*, **93**, 2804 (1971); K. Mizuno, C. Pac, and H. Sakurai, *ibid.*, **96**, 2993 (1974).

(36) A referee has expressed concern for the requirement of highly efficient closure of the exciplex (about 30 to 60% using the projected efficiency of excimer formation). Though we have not specifically included such a reaction in our mechanism, we cannot rule out the possibility that TME intercepts $^1C^*$ with very low efficiency, and of course the extent to which this occurs would reduce the overall demand for exciplex closure. It should be noted that the quantum efficiencies we have observed for other olefins are considerably smaller than TME (see below).

(37) Representative recent references include: (a) B. S. Solomon, C. Steel, and A. Weller, *Chem. Commun.*, 927 (1969); (b) T. R. Evans, *J. Amer. Chem. Soc.*, **93**, 2081 (1971); (c) G. N. Taylor, *Chem. Phys. Lett.*, **10**, 355 (1971); (d) N. C. Young, M. H. Hui, and S. A. Bellard, *J. Amer. Chem. Soc.*, **93**, 4056 (1971); (e) D. A. Labianca, G. N. Taylor, and G. S. Hammond, *ibid.*, **94**, 3679 (1972); (f) K. H. Grellman, A. R. Watkins, and A. Weller, *J. Phys. Chem.*, **76**, 469 (1972), and other papers in this series; (f) F. D. Leis and R. H. Hirsch, *Tetrahedron Lett.*, 4947 (1973); (h) M. P. Niemczyk, N. E. Schore, and N. J. Turro, *Mol. Photochem.*, **5**, 69 (1973); (i) P. A. Hackett and D. Phillips, *J. Phys. Chem.*, **78**, 679 (1974).

(38) Using the value for *trans*-2-hexene; *cf. Nat. Stand. Ref. Data Ser., Nat. Bur. Stand.*, **No. 26** (1969).

(39) The cycloadducts from TH could not be obtained completely pure. Two were formed from EVE and identified as the syn and anti head-to-tail isomers.[2]

(40) All these olefins effectively eliminate IIa formation (coumarin IP, 11.3 eV),[41] so the data reported were obtained by competition experiments. Such numbers will also reflect the relative efficiencies of eq 26 *vs.* eq

27 for the different olefins, and more quantitative Stern–Volmer data are needed.
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(42) S. Farid, J. C. Doty, and J. L. R. Williams, *J. Chem. Soc., Chem. Commun.*, 711 (1972).
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(44) *trans*-2-Heptene is the only one of the three olefins which does not completely quench the triplet derived dimer (IIb). See also ref 8.
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A Total Synthesis of *dl*-Camptothecin

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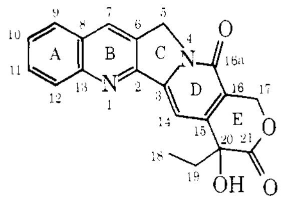
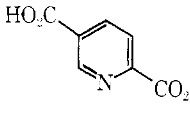
Abstract: *dl*-Camptothecin has been synthesized in 15% overall yield from isocinchomeronic acid. The synthetic design incorporates three rearrangements: rearrangement of a nipecotic acid to an α-methylenelactam, selenium dioxide oxidation of an olefin to an allylic alcohol and acid catalyzed rearrangement of the latter, and Claisen rearrangement involving an allylic alcohol-orthoester system. Thus, isocinchomeronic acid was converted to 1-acetoxy-6-methylene-5-oxooctahydroindolizine *via* 1-oxooctahydroindolizine-6-carboxylic acid in 62% yield. Allylic oxidation-rearrangement led to 1-hydroxy-6-hydroxymethyl-5-oxo-Δ^6-hexahydroindolizine (43%), and the α-butyrate side chain was then introduced by Claisen rearrangement with trimethyl orthobutyrate. The 1-hydroxyl was oxidized to keto and condensed with *N*-(2-aminobenzylidene)-*p*-toluidine to give the tetrahydroindolizino[1,2-*b*]quinoline. Selenium dioxide in acid gave both allylic oxidation-rearrangement and aromatization to the pyridone. Acid catalyzed lactonization and α-hydroxylation (O_2-$CuCl_2$-DMF) of the lactone completed the synthesis.

Camptothecin (**1**) is a novel alkaloid originally isolated from *Camptotheca acuminata* (Nyssaceae)[1] and more recently from *Mappia foetida* Miers (Olacaceae).[2] Its structural elucidation was accomplished in 1968[3] and with the initial report of its potent antileukemic and antitumor activity,[4] many attempts were made to synthesize camptothecin, culminating in a number of successful total syntheses.[5]

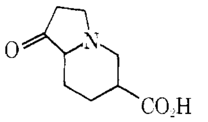


1

Our approach to the synthesis of camptothecin, a preliminary account of which has appeared,[1e] was based fundamentally on the bicyclic ketoacid 1-oxooctahydroindolizine-6-carboxylic acid (**3**), which was obtained as the hydrochloride in 85% yield from an inexpensive, commercially available starting diacid, isocinchomeronic acid (**2**). The choice of the bicyclic ketoacid was made with the knowledge that the characteristic 2-pyridone D ring of camptothecin (**1**) can be introduced by a simple rearrangement of a nipecotic acid to an α-methylenelactam.[6] The resulting 3-methylene-2-piperidone, after appropriate substitution, can subsequently be oxidized to a pyridone.



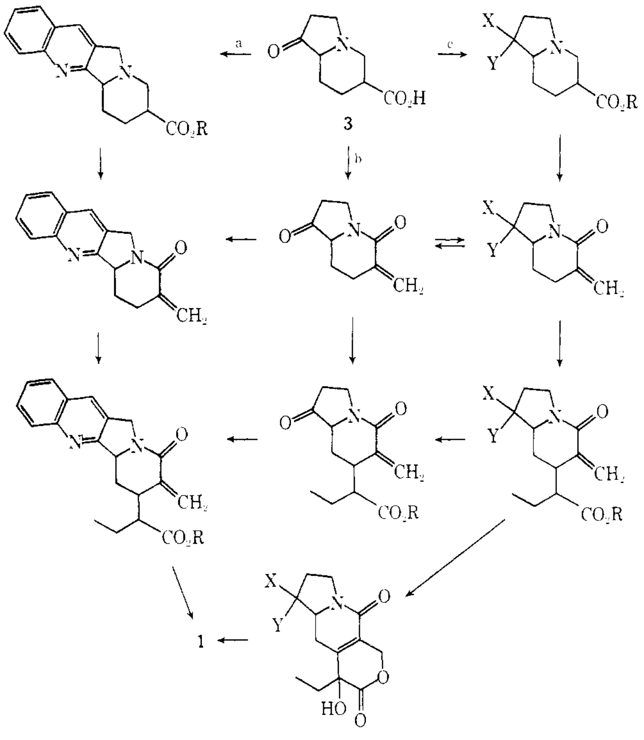
2



3

From bicyclic ketoacid **3** the overall synthesis consists of three phases: (i) α-methylenelactam rearrangement of a nipecotic acid, (ii) introduction of the quinoline AB rings *via* the Friedländer condensation, and (iii) oxidation of the α-methylenelactam to an allylic alcohol followed by introduction of the butyrate residue at the 4-position of the piperidone D ring, oxidation, and lactonization. As Scheme I shows, the sequence need not be in this order for the synthesis was designed to allow maximum flexibility before converging on camptothecin.

Scheme I. Convergent Routes for Camptothecin Synthesis from **3**



R = H, alkyl
X,Y = H, OH, or OR′

Preparation of bicyclic ketoacid **3** from isochinchomeronic acid (**2**) was begun by hydrogenation of **2** in aqueous ammonia using 5% rhodium on alumina catalyst following a