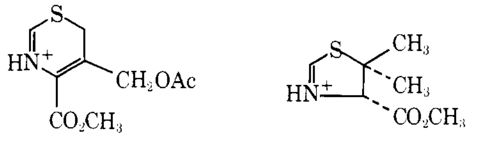
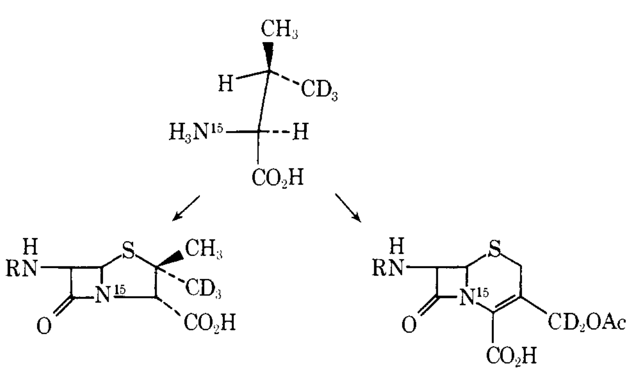
Table I. Isotopic Distribution of Cephalosporin C and Penicillin N Derivatives Derived from (2*S*, 3*S*)-Methylvaline-^{15}N,*3-methyl-*d_3



m/e 230 *m/e* 174

m/e	Ceph C	*m/e*	Pen N
230	63.2	174	63.4
231	6.5	175	2.0
232	24.1	176	1.6
233	6.2	177	27.6
		178	5.4

transamination to a considerable extent as indicated by the appearance of (P + 3) and (P + 1) peaks for penicillin N and (P + 2) and (P + 1) peaks for cephalosporin C. As the isotopic ratios of the valinyl moieties in both penicillin N and cephalosporin C were found to be very similar, this finding is consistent with the proposition that both β-lactam antibiotics originate from a common tripeptide intermediate such as ACV.



We next turned our attention to the question whether α,β-dehydroamino acid units are involved during the incorporation of L-valine into ACV, since an α,β-dehydrovaline derivative of a tripeptide has been proposed as a possible common intermediate in the biosynthesis of penicillin and cephalosporin antibiotics.[15-17] As cell extracts of *C. acremonium* incorporated only small quantities of L-valine-^{14}C into ACV, uniformly labeled L-valine-^{14}C (20 μCi)[18] was exposed to washed starved cells of *C. acremonium*[11] for 15 min to yield ACV-^{14}C (0.36 μCi), which was isolated as its sulfonic acid derivative.[2] After acid hydrolysis, the radioactive valine (0.19 μCi) was isolated and its absolute configuration was confirmed to be that of D configuration by use of L- and D-amino acid oxidases.[11] In a similar fashion, L-[2,3-^{3}H]valine (40 μCi)[18] was fed and the resulting tritiated ACV (0.4 μCi) was isolated and hydrolyzed with acid. The tritiated valine (0.2 μCi) thus produced was again exposed to L- and D-amino acid oxidases. The results clearly show that only the tritium atom at C-3 of the L-[2,3-^{3}H]valine is retained during its incorporation into ACV, for the tritium content of the valinyl residue (7000 cpm), derived from ACV, was about the same as that of the α-ketovaleric acid (6750 cpm), obtained upon oxidation with D-amino acid oxidase. Although the intimate details of the epimerization of the α-center of valine remain to be established, our data are incompatible with reaction mechanisms involving α,β-dehydrovalinyl intermediates or direct internal hydride shift, common among hydroxy acid racemases.[19]

These results, and the observation that tritiated ACV, labeled at the α-center of the D-valinyl moiety, was incorporated into penicillin N by protoplast lysates of *C. acremonium* with retention of tritium,[5] provide cogent evidence against the participation of free α,β-dehydrovalinyl tripeptide intermediate(s) in the formation of the penam nucleus.

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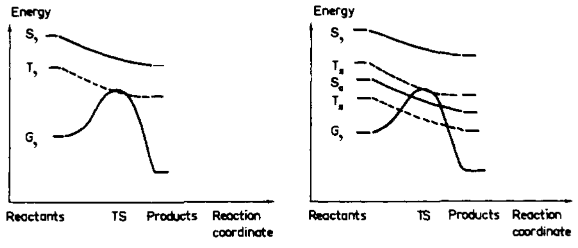
Chemiexcitation Mechanisms. The Role of Symmetry and Spin-Orbit Coupling in Diradicals

Sir:

For a Woodward–Hoffmann symmetry-forbidden pericyclic reaction, Figure 1a shows schematically the three potential energy surfaces connecting the ground (G), lowest



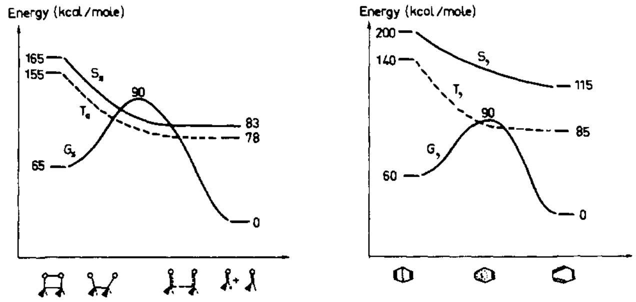
1a 1b

Figure 1. General pattern of potential energy surfaces for forbidden pericyclic reactions when the lowest (singlet–triplet) excited states of reactants and products are symmetric (1a) or antisymmetric (1b) with respect to the plane containing t reaction centers.

excited triplet (T), and singlet (S) states of reactants and products.[1] (The subscript S must be ignored for the moment.) The salient characteristics of this correlation diagram near the transition state geometry (TS) are: (a) the near-degeneracy and the "diradical" character[2] of the "forbidden" ground state G and the lowest triplet T and (b) the substantial energy separation between the "zwitterionic" singlet state S and the diradical states G and T.[3]

Let us consider more specifically here those forbidden pericyclic reactions where the plane P of the pertinent reaction centers is an additional symmetry element.[4] This will allow us to classify the important molecular orbitals as π or σ. For these reactions the wave functions of the G, T, and S states are generally *totally symmetric* with respect to P. These three states can then be assigned the same symmetry designations (Figure 1a). If both reactants and products also possess a (singlet–triplet) pair of *antisymmetric* states (S_a and T_a) *lower* in energy than T_s, the full correlation diagram may be represented as in Figure 1b. In contrast to the situation in Figure 1a, Figure 1b shows that there are now two additional potential energy surfaces whose energies are lower than or comparable to that of the ground state in the transition region. Four additional crossing points are then expected, each of the T_a and S_a surfaces crossing the G_s surface twice.

All the "first-order" crossings should be relevant to chemiexcitation since, for each of them, the energetic situation is most favorable for a switch from the initial ground-state surface (G_s) to an excited state surface (T_a, S_a, and, eventually, T_s). Let us note that in actual examples these "first-order" allowed crossings will become weakly avoided because of any one of several factors such as failure of the system to possess the true plane of symmetry which was postulated in our analysis or the occurrence of perturbations (for example the spin–orbit coupling terms) which were not explicitly taken into account in our simple model.[5] In a *thermal* process the reactants might switch at these crossing points from their ground state surface to any one of the T_a, S_a, and, eventually, T_s surfaces. The (G_s, T_a) crossing will be more "populated" than the (G_s, S_a) crossing. The (G_s, T_s) crossing will obviously be the most difficult to reach. On the other hand the probability of these radiationless transitions depends both on electronic and vibrational factors.[6] For transitions between states of similar multiplicity ($G_s \rightarrow S_a$ internal conversion) the *electronic* coupling results from bielectronic repulsion terms and/or vibronic interaction terms. For transitions between states of different multiplicity ($G_s \rightarrow T_a$ or T_s intersystem crossing) the *electronic* coupling element is the spin–orbit Hamiltonian. El-Sayed has shown that both electronic *and* vibrational factors favor singlet–triplet transitions involving states of "opposite" symmetry (for example $S_{\pi\pi^*} \rightarrow T_{n\pi^*}$ or, in the present case, $G_s \rightarrow T_a$). These transitions are 10^2 to 10^3 times faster than those involving states of similar spatial symmetry (for example $S_{\pi\pi^*} \rightarrow T_{\pi\pi^*}$ or, in the present case, $G_s \rightarrow T_s$).[7] Thus we may conclude that the two "jumps" $G_s \rightarrow T_a$ and $G_s \rightarrow S_a$ will compete to switch the reacting species from their ground state to an excited state. The $G_s \rightarrow T_a$ crossing is easier to reach thermally but the corresponding transition probability suffers from small electronic (spin–orbit) coupling terms. The $G_s \rightarrow S_a$ crossing is more difficult to attain thermally but the transition probability is larger (bielectronic terms).

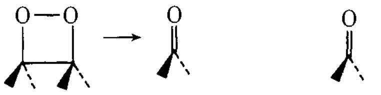


2a 2b

Figure 2. Pattern of potential energy surfaces for the retrocycloaddition reaction of dioxetanes (2a) and the electrocyclic conversion of Dewar benzene to benzene (2a).

Thus if the pattern of the various potential energy surfaces of a ground-state forbidden pericyclic reaction can be shown from spectroscopic data to correspond to Figure 1b, a favorable case for chemiexcitation exists because of the occurrence of two pathways which take the initial system in its ground state to intersections with excited state potential energy surfaces which, ultimately, correlate with excited states of the products. *As a result a model is available which predicts, without reference to a detailed calculation, the points where the switch from the ground state surface of the reactants to an excited state surface of the products is most likely to occur* ($G_s \rightarrow T_a$ or S_a).

As a specific application of these ideas let us consider the thermally forbidden $\sigma 2 + \sigma 2$ retrocycloaddition of dioxetanes into two carbonyl fragments[8] (eq 1, P is the plane of


(1)

the paper). The appropriate state correlation diagram is shown in Figure 2a.[9] The lowest triplet and singlet excited states of dioxetane result from the promotion of one electron from the OO antibonding π^* orbital to the OO antibonding σ^* MO.[10] These $\pi^* \rightarrow \sigma^*$ states are antisymmetric with respect to the plane P of the molecule (T_a and S_a) whereas the ground-state is totally symmetric (G_s). The lowest singlet and triplet states of acetone are antisymmetric $n\pi^*$ states. Their symmetry is also opposite to that of the symmetric ground state.[11] In addition spectroscopic data lead us to expect intersections of the S_a and T_a surfaces with G_s as the reaction proceeds. This reaction follows a stepwise biradical mechanism starting with the elongation of the OO bond.[12] In the first crossing regions (on the left-hand side of Figure 2a) the electronic structure of the various states is typical of a *tetratopic* reaction.[13] Four radical centers (one σ and one π radical center on each oxygen, atoms A and B) and four pairs (singlet, triplet) of diradical configurations ($\sigma_A\sigma_B$, $\sigma_A\pi_B$ and $\sigma_B\pi_A$, $\pi_A\pi_B$, see Figure 3) are therefore expected. The ground state G_s mainly corresponds to the $\sigma_A\sigma_B$ configuration with a small admixture of $\pi_A\pi_B$ which has the same overall symmetry (s). The lowest pair of antisymmetric states (S_a and T_a) results from the *in-*

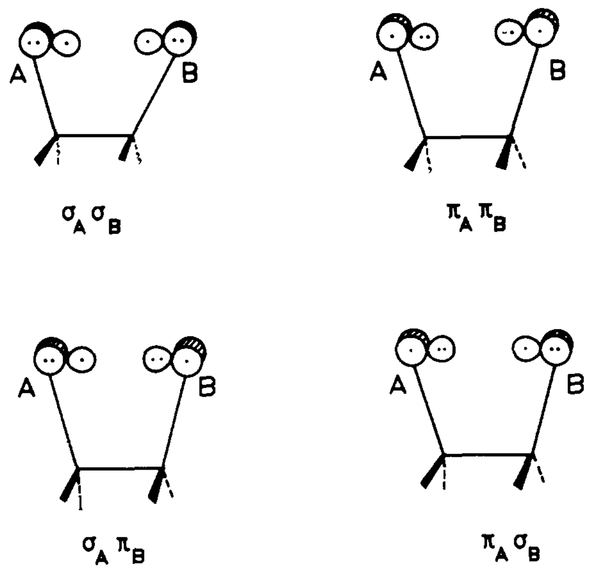
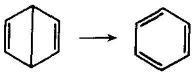


Figure 3. The four diradicals (singlet or triplet) created when the dioxetane OO bond is stretched (the two lobes of the π orbital on the oxygen atoms are represented, the second one being shaded: the σ orbitals are parallel to the CC bond).

phase combination of the $\sigma_A\pi_B$ and $\sigma_B\pi_A$ pairs. A decisive factor in the chemiexcitation of dioxetane is that the lowest triplet $T_a(^3\sigma_A\pi_B + {}^3\sigma_B\pi_A)$ and the "ground state" singlet G_s ($\sigma_A\sigma_B$) are strongly spin-orbit coupled.[14] *This gives the lower energy but spin-forbidden* $G_s \rightarrow T_a$ *pathway an excellent opportunity to occur in competition with or even in preference to the high energy but spin-allowed* $G_s \rightarrow S_a$ *pathway.* Indeed since the analogous $^1n\pi^*$ (antisymmetric) $\rightarrow$ $^3\pi\pi^*$ (symmetric) transition occurs with a rate constant of 10^{10} to 10^{11} sec^{-1} for benzophenone,[15] it is likely that the $\sigma\sigma \rightarrow \sigma\pi$ transition in our example will possess a comparable or faster rate. Thus the rate of intersystem crossing from G_s to T_a could well be of the order of magnitude expected for ordinary transition states.[16] At the second (T_a, G_s) intersection (on the right-hand side of Figure 2a) the reverse transition $T_a \rightarrow G_s$ is much less likely. Here the breaking of the CC bond is well under way. The σ_A and σ_B oxygen orbitals are now delocalized over the carbon atoms (to give the familiar π orbitals of acetone). As a result the one-center contributions[14] in the spin-orbit matrix elements decrease.[17] The probability for the system to remain on the triplet surface at least competes with that for the system to "jump" to the G_s surface. The model thus makes understandable the observation that 1,2-dioxetanes cleave effectively into triplet products.

Let us now briefly consider a second example: the $\sigma^2 + \pi^2$ conversion of Dewar benzene to benzene (eq 2).[18] Dewar

 (2)

benzene is not planar and its reaction is basically analogous to the opening of cyclobutene to butadiene.[4] The plane of the four reacting carbon centers is *not* a plane of symmetry for the whole reaction. If we, however, *suppose* Dewar benzene to be planar a better understanding of its chemiexcitation may be gained. The (hypothetic) plane of the molecule becomes the additional symmetry element we need to classify the relevant states as s or a. The corresponding correlation diagram is represented in Figure 2b.[19] The only possible site for a singlet–triplet jump is the transition state region where G_s and T_s are in a "touching" situation.[13] In this case, however, both states have the same symmetry, and the switch is not favored by symmetry as was the case for (1). We should expect, therefore, the efficiency of formation of triplet species to depend on the rate of intersystem crossing relative to the rate of decay of species whose structures and energies are comparable to those of the transition state for the forbidden pericyclic reaction. Employing a rate of 10^{11} sec^{-1} as typical for transition state lifetimes and 10^7 sec^{-1} for the $G_s \rightarrow T_s$ conversion,[20] we expect the nonadiabatic efficiency to be of the order of 10^{-4}, as found experimentally.[18] Furthermore the introduction of heavy atoms in the Dewar structure should enhance the intersystem crossing rate, resulting in a higher chemiexcitation efficiency. This is also observed experimentally.[18,21]

The description we have presented is primarily based on electronic arguments, i.e., the current theories of forbidden per cyclic reactions and the mechanism of spin inversion in diradicals. The densities of vibronic states in the crossing regions and the vibrational overlap matrix elements will be also decisive factors in the comparison of the various pathways and should be considered as well.[22] Nevertheless this simple model allows an understanding of the occurrence, the efficiency and the multiplicity selectivity of the nonadiabatic reactions involved in chemiluminescence.

Acknowledgements. N.J.T. thanks the Air Force Office of Scientific Research and NSF for financial support. Both authors are grateful to Professor L. Salem for many helpful discussions.

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(4) In the $\sigma^2 + \sigma^2$ retrocycloaddition of dioxetanes into two carbonyl fragments, the plane of the reaction centers—the CCOO plane—is such an additional symmetry element which is retained throughout the reaction. However, in the disrotatory cyclization of butadiene to cyclobutene, the plane of the four carbon atoms is *not* such a symmetry element conserved during the reaction. In this second example the only symmetry element which is conserved is the usual Woodward–Hoffmann plane of symmetry which bisects the newly formed σ and π cyclobutene bonds.

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(10) D. R. Kearns, *J. Am. Chem. Soc.*, **91**, 6554 (1969).

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(12) W. H. Richardson, F. C. Montgomery, M. B. Yelvington, and H. E. O'Neal, *J. Am. Chem. Soc.*, **96**, 7525 (1974).

(13) The concept of "topicity" was first introduced in the case of "bitopic" and "tritopic" photochemical reactions by L. Salem, *J. Am. Chem. Soc.*, **96**, 3486 (1974), and has been recently generalized: W. G. Dauben, L. Salem, and N. J. Turro, *Acc. Chem. Res.*, **8**, 41 (1975).

(14) The matrix elements of the spin–orbit Hamiltonian H_{SO} between the triplet configurations $\sigma_A\pi_B$ or $\sigma_B\pi_A$ and the singlet ground state configuration are equal and proportional to the one-center integral $\langle\sigma_A|H_{SO}|\pi_A\rangle$.

The *in-phase* combination of the two triplet configurations and the singlet ground state are then coupled by a spin–orbit term which is proportional to $2\,\langle\sigma_A|H_{SO}|\pi_A\rangle$. On the other hand the two equal one-center integrals occurring in the coupling between the *out-of-phase* combination of the two triplet configurations and the ground state cancel each other. Note also that this second combination is much higher in energy and certainly does not cross the G_s surface.

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(16) The lifetime of a transition state is generally taken to be 10^{-12} to 10^{-13} sec for relatively simple molecules: A. A. Frost and R. G. Pearson "Kinetics and Mechanism", Wiley, New York, N.Y., 1965, p 77.

(17) As pointed out by one of the referees the π molecular orbital of acetone may be approximately described as $(\sigma_A + \sigma_C)/\sqrt{2}$. The term which couples ${}^3\sigma_A\pi_B$ and ${}^1\sigma_A\sigma_B$ then becomes $\frac{1}{2}\,\langle\sigma_A|H_{SO}|\pi_A\rangle$. Since the probability of a radiationless transition is proportional to the square of the electronic (spin–orbit) coupling term,[6] the probability of the $T_a \rightarrow G_s$ transition will be roughly one-fourth of the $G_s \rightarrow T_a$ transition probability.

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(22) For example there is no one-center term coupling the singlet and triplet $n\pi^*$ states in aliphatic ketones. Still the rate of the corresponding radiationless intersystem crossing is large (10^7 sec^{-1}).

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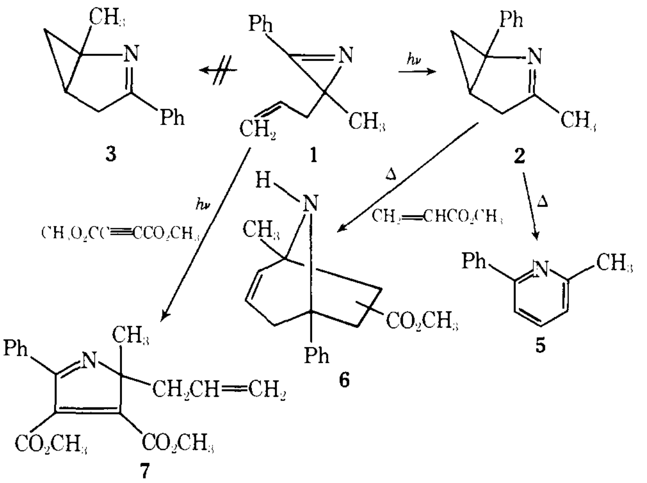
1,1-Cycloaddition from a 1,3-Dipole[1]

Sir:

Huisgen and coworkers were the first to recognize fully the general concept and scope of 1,3-dipolar cycloadditions,[2-4] a reaction of considerable merit for the synthesis of five-membered heterocyclic rings. Our research group has recently investigated the 1,3-dipolar cycloaddition reactions of nitrile ylides generated by photolysis of arylazirines.[5,6] Nitrile ylides may be classified as nitrilium betaines, a class of 1,3 dipoles containing a central nitrogen atom and a π-bond orthogonal to the 4π-allyl system. Among the possible resonance forms of a nitrile ylide, a carbene structure can be envisioned which makes conceivable a 1,1 cycloaddition of this 1,3 dipole.[7] We report herein the first example of such a cycloaddition.

In order to establish the orientation of the intramolecular 1,3-dipolar cycloaddition reactions of nitrile ylides, we chose to investigate the photochemistry of 2-phenyl-3-methyl-3-allylazirine (**1**).[8] When a thoroughly deaerated solution of **1** was irradiated in cyclohexane with light of wavelength >250 nm, an extremely rapid and clean conversion to 1-phenyl-3-methyl-2-azabicyclo[3.1.0]hex-2-ene (**2**) was observed. The identity of **2** was determined by its straightforward spectral characteristics [ir (neat) 1640 cm^{-1}; NMR (100 MHz) τ 9.64 (t, 1 H, J = 5.0 Hz), 8.68 (dd, 1 H, J = 8.0 and 5.0 Hz), 8.33 (m, 1 H), 8.13 (s, 3 H), 7.64 (d, 1 H, J = 17.5 Hz), 7.22 (dd, 1 H, J = 17.5 and 8.0 Hz), 2.61-3.10 (m, 5 H)] as well as its facile conversion to 2-methyl-6-phenylpyridine (**5**) (picrate 131-132°)[9] on heating. When the thermolysis of azabicyclohexene **2** was carried out in toluene in the presence of methyl acrylate, azabicyclo[3.2.1]octene (**6**); mp 87-88°, was isolated in good yield [NMR (100 MHz) τ 8.68 (s, 3 H), 7.76 (dd, 1 H, J = 18.0 and 4.0 Hz), 7.48 (m, 3 H), 6.82 (dd, 1 H, J = 7.0 and 4.0 Hz), 6.36 (s, 3 H), 4.34 (ddd, 1 H, J = 9.5, 4.0, and 2.0 Hz), 4.14 (dt, J = 10.0 and 1.5 Hz), 2.4-2.8 (m, 5 H)]. The formation of this adduct is readily interpreted if it is assumed that **2** undergoes an initial 1,3-proton shift to give 1-phenyl-3-methyl-2-azabicyclo[3.1.0]hex-3-ene which subsequently undergoes cycloaddition with the added dipolarophile. Tanny and Fowler[10] have recently shown that the 2-azabicyclo[3.1.0]hex-3-ene ring system will undergo thermal cycloaddition reactions with electron-deficient olefins, thereby providing good analogy for the last step of the proposed sequence.



The ultraviolet spectrum (cyclohexane) of the photoproduct showed a maximum at 225 nm which is compatible with structure **2** but not with the isomeric azabicyclohexene **3**.[11] Photolysis of **1** in the presence of excess dimethyl acetylenedicarboxylate resulted in the trapping of a nitrile ylide and afforded cycloadduct **7**, mp 58-60°, in high yield. Under these conditions, the formation of **2**, which is produced in quantitative yield in the absence of a trapping reagent, is entirely suppressed.[12,13] Similar results were obtained when methyl acrylate was used as the trapping reagent.

The photoreactions of the closely related methyl-substituted azirines **8** and **12** were also studied in order to assess the generality of the photocycloaddition reaction. Irradiation of **8** in cyclohexane afforded a quantitative yield of 1-phenyl-3,4-dimethyl-2-azabicyclo[3.1.0]hex-2-ene (**9**) as a mixture of endo (25%) and exo (75%) isomers. The NMR of the major isomer [(100 MHz) τ 9.62 (t, 1 H, J = 4.6 Hz), 8.92 (d, 3 H, J = 8.0 Hz), 8.66 (dd, 1 H, J = 8.0 and 4.6 Hz), 8.42 (dd, 1 H, J = 8.0 and 4.6 Hz), 8.12 (s, 3 H), 7.48 (1 H, q, J = 8.0 Hz), 2.4-3.0 (m, 5 H)] showed the two cyclopropyl protons expected for structure **9** but not for the isomeric azabicyclohexene **10**.[14] The initial photoproduct was smoothly converted to 2,3-dimethyl-6-phenylpyridine (**11**) on heating. Structure **11** was verified by comparison with an authentic sample.[15] The formation of **9** could be completely suppressed when the irradiation of **8** was carried