

**Scheme 1.** Thermochemical and photochemical profiles of 2-picolyl chloride.

When a hydrogen of 2-methyl pyridine is substituted by  $\text{CH}_3\text{O}$ , *iso*-PrO, and EtO group, it did not undergo photoisomerization to the corresponding aniline or para-substituted pyridines within the range of the time used for 2-picolyl chloride (chemical yield; 0) as checked by TLC and NMR spectrum. When chlorine atom is substituted by CN, COOMe, or Ph, the formation of Dewar pyridines is facilitated because the two methylene hydrogens are activated by the double bonds or the triple bond at the both sides. These hydrogens are at allylic position for two double bonds (or a double bond and a triple bond) at both sides. Since no aniline is obtained

in the case of 2-Py $\text{CH}_3$ <sup>8</sup> and 2-Py $\text{CH}_2\text{Cl}$ , the formation of Dewar pyridines is not likely and the photoisomerization of these compounds to parasubstituted picoline and 4-picolyl chloride occurs probably through prismane intermediates as summarized in scheme 1.

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## Photocyclodimerization of Maleimide

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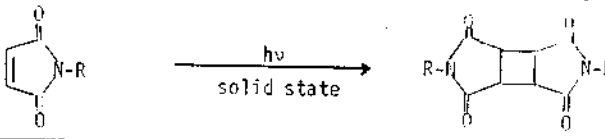
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The photoreaction of maleimide, one of the best model compounds of DNA molecules for psoralen-DNA photoreactions, is studied in order to investigate the photoreactivity and the mechanism of the maleimide-psoralen photoreaction. The (2+2) photocyclodimer of maleimide was obtained in solution state by direct or sensitized irradiation. The rate constant of dimerization is determined by quenching studies and found to be of the order of  $10^9 \text{ M}^{-1}\text{sec}^{-1}$ . The direct dimerization of maleimide is found to undergo through the triplet excited state. The quantum yields of dimerization are dependent on the maleimide concentration.

### Introduction

The (2+2) photocyclodimerization of maleic anhydride and maleimide derivatives has been studied by several groups.<sup>1-8</sup> Maleic anhydride has been reported to photodimerize in the crystalline state.<sup>9,10</sup> Schenck *et al.*<sup>1</sup> reported that the photodimerization of dimethylmaleic anhydride in benzene was photosensitized by benzophenone. Under this condition (which differed mainly in the use of a medium-

rather than a high-pressure mercury arc lamp), the consistent addition of benzophenone slightly reduced the rate of dimerization. The known photodimer of dimethylmaleic anhydride was shown, on chemical and crystallographic evidence, to have *trans* structure.<sup>4</sup> The spectral data of photodimer of N-substituted maleimides are shown in Table I. However, crystal structure analysis of the monomer indicates neither parallel double bonds nor contacts between two monomer units at distances adequate for photodi-

**TABLE 1:**  $^1\text{H}$  NMR Chemical Shifts of Photodimer of *N*-Substituted Maleimides


R	NMR <sup>a, b</sup>
C <sub>6</sub> H <sub>5</sub>	3.96 (DMSO-d <sub>6</sub> /HMDS)
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	4.02 (DMSO-d <sub>6</sub> /HMDS)
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	3.94 (DMSO-d <sub>6</sub> /HMDS)
(CH <sub>2</sub> ) <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	3.12 (CDCl <sub>3</sub> /TMS)
	3.08 (CHCl <sub>2</sub> COOH/HMDS)

<sup>a</sup> *J. Polym. Sci.*, **13**, 201 (1975). <sup>b</sup> Resonance signals of the cyclobutane ring protons; all signals are singlet.

merization.<sup>11</sup> Moreover, the photodimerization in the solid state is completely inhibited at temperatures higher than 5 °C.

Particularly, the photodimerization of *N*-butylmaleimide was studied in detail by Put and De Schryver.<sup>7</sup> In the dimerization of *N*-butylmaleimide, two isomers can be formed; one in which the two maleimide rings lie at the same side of the cyclobutane ring (endo) and one in which the two maleimide rings lie at opposite side (exo). Under the reaction conditions (in CH<sub>2</sub>Cl<sub>2</sub>), only the exo isomer was formed, as was confirmed by comparison of the signal of the cyclobutane protons in NMR of the dimer and that of the corresponding protons of the cyclomers of dimaleimides.

But, especially in benzene solution, (2+2) photodimer of maleimides was not formed but only photoadduct of maleimides to benzene was formed.<sup>12-15</sup> Maleimide and some, but not all, *N*-substituted maleimides readily form 2:1 photoadducts with benzene. The reactions can be weakly photosensitized by benzophenone. The 2:1 photoadducts have been formed from maleimide, *N*-benzyl-, *N*-*o*-tolyl- and *N*-2,6-xylylmaleimide. *N*-phenyl-, *N*-*p*-tolyl- and *N*-*p*-methoxyphenylmaleimide did not form 2:1 photoadduct with benzene.<sup>12</sup>

Maleimides are the heterocyclic compounds having a conjugated double bond with two carbonyl functional groups. It has been shown that maleimide has a strong quenching effect on the triplet state of the furocoumarins although the cycloadducts are formed with low quantum yields. The equilibrium constants of molecular complex formation in the ground state between psoralens and maleimide are comparable to those of psoralens-DNA complex formation. Furthermore, the initial rate of photocycloaddition reaction between psoralens and maleimide yielding a fluorescent product, probably formed by 2+2 addition of 4',5'-furyl double bond of psoralens to maleimide, is same as that of psoralens-DNA photoreaction on long wavelength UV irradiation. Thus, maleimide appears to be a better model compound for DNA than pyrimidine bases such as thymine and cytosine in the photoreactions of psoralen and DNA *in vitro*.<sup>16, 17</sup>

Although photodimerization of maleic anhydride and several maleimide derivatives were carried out by Schenck

and coworkers, the photochemical information such as quenching experiments or kinetic data are not available for unsubstituted maleimide. Unsubstituted maleimide can exist in several tautomeric forms unlike *N*-substituted maleimides and the photoreaction of unsubstituted maleimide may differ from that of *N*-substituted maleimides. In order to elucidate the mechanism of the photoreaction of psoralens-maleimide, we undertook a thorough study of the photodimerization of unsubstituted maleimide.

## Materials and Method

**Materials.** Extra pure acetonitrile, acetone, ethyl acetate, methanol, and chloroform (Wako Chemical Co. or Cica Chemical Co.) were used as received or after distillation. Maleimide was synthesized according to the method reported by Tawney *et al.* (1960)<sup>18</sup> The purified maleimide can be recrystallized from ethyl acetate or chloroform. This recrystallization was repeated if necessary. The compound used in the kinetic experiments was further purified by sublimation. Benzophenone, acetophenone and biacetyl (2,3-butadione) were obtained from Aldrich or Sigma Chemical Co.

**Irradiation Apparatus.** Irradiations were carried out in a Rayonet Photochemical Reactor (The Southern New England UV Co.) Model RPR-208 or RPR-100 equipped with 350 nm lamps. A merry-go-round unit with 450W Hanovia medium pressure mercury arc lamp (Type 679A36) was used for comparative study.

**Spectroscopic Measurements.** Ultraviolet-visible spectra between 200 nm and 400 nm were recorded using a Cary 17 spectrophotometer. Infrared spectra were recorded in KBr pellets on a Perkin-Elmer 267 grating spectrophotometer. Nuclear magnetic resonance spectra were measured on a Varian T-60A spectrometer in D<sub>2</sub>O with sodium carbonate or chloroform-*d*. The mass spectra were determined with Hewlett Packard 5985 A GC-MS system by electron impact method.

**Irradiation and Product Isolation. Direct Irradiation:** Maleimide was dissolved in chloroform or acetonitrile to obtain 10<sup>-2</sup> M concentration of maleimide. The solution was deoxygenated by bubbling with dry nitrogen for 2 h and irradiated for about 10 h in a preparative photochemical reactor equipped with UV lamps (RPR-208, 350 nm lamps). After irradiation, the major product was isolated by filtering followed by column chromatography. The product was characterized by spectroscopic methods. **Sensitized Irradiation:** Maleimide and benzophenone or acetophenone were dissolved in chloroform or acetonitrile to obtain 10<sup>-2</sup> M of maleimide. Then, benzophenone or acetophenone (sensitizer) was dissolved to make the absorbance at 350 nm greater than 2. The sample was irradiated by the same method used in the direct irradiation.

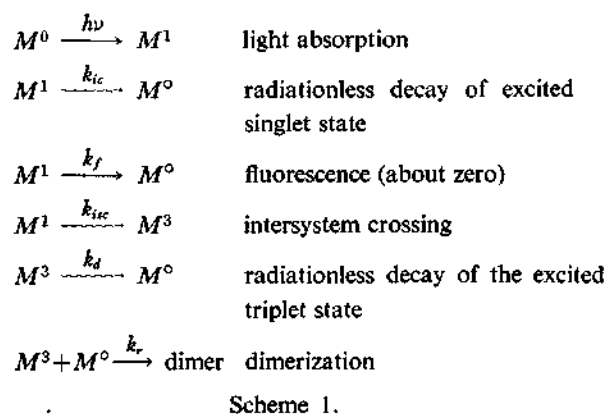
**Quantum yield of the dimerization.** A series of solutions (3 ml) with different concentrations of maleimide in acetonitrile were put into a Pyrex ampoule and degassed by five freeze-pump-thaw cycles (<10<sup>-4</sup> mmHg) with cooling in liquid nitrogen and then sealed. Thus prepared samples

were irradiated in a merry-go-round unit with 450 W Hanovia medium pressure mercury arc lamp (Type 679A36). A Corning glass filter of #7-54 and a solution filter of  $2.5 \times 10^{-3} M$  potassium chromate in 1% sodium carbonate aqueous solution were used to get a monochromatic light of 313 nm. The temperature in the reactor was maintained at 15°C. The light intensity was measured by tris (oxalato) ferrate (III) actinometry.<sup>19</sup> The amount of photochemical  $C_4$ -cyclodimers were analyzed by UV spectrophotometer at 270 nm.

**Quenching Studies on the Dimerization.** A series of solutions (3 ml) of different concentration of maleimide and varying biacetyl concentrations, were put into a Pyrex ampoule and degassed by four freeze-pump-thaw cycles with cooling in liquid nitrogen and then sealed. The samples were irradiated by the same method used in the measurements of quantum yield of the dimerization. Biacetyl absorbed less than 2% of the light and maleimide concentration should be higher than  $1.0 \times 10^{-3} M$ . The conversion in each sample was determined by the measurement of the maleimide absorbance at 270 nm. The change in absorbance of each sample was compared with that of the reference sample containing no biacetyl.

## Results and Discussion

**Mechanism of Dimerization.** The absolute quantum yields of dimerization were measured and shown in Table 2. Scheme 1 can be written for the photochemical processes occurring in this system..



Therefore, the quantum yield for the dimerization is:

$$\Phi_{\text{DIM}} = \Phi_{\text{isc}} \frac{k_r[M]}{k_r[M] + k_d}$$

And

$$1/\Phi_{\text{DIM}} = 1/\Phi_{\text{isc}} \left( 1 + \frac{k_d}{k_r[M]} \right)$$

A plot of  $1/\Phi_{\text{DIM}}$  vs. reciprocal of maleimide concentration gave a good straight line indicating that the proposed mechanism was correct.

Since the rate of the formation of the dimer is first order in maleimide concentration, the lifetime of the excited state of maleimide depends on the maleimide concentration as described by eq. (1), where  $k_d$  and  $k_r$  are the rate constants

TABLE 2: Quantum Yields of Photodimerization of Maleimide

Maleimide concentration ( $\times 10^{-3} M$ )	$\Phi_{\text{DIM}}$ ( $\times 10^2$ )	$1/\Phi_{\text{DIM}}$
10	8.7	11.5
5	5.9	17.0
1	1.0	99.0
0.5	0.48	208.3

TABLE 3: Quenching of the Photodimerization of Maleimide with Biacetyl

Maleimide concentration ( $\times 10^{-3} M$ )	$k_q\tau$ ( $M^{-1}$ )	$\tau \times 10^8$ (sec)	$1/\tau \times 10^{-7}$ ( $\text{sec}^{-1}$ )
10	401	2.4	4.2
5	521	3.1	3.3
1	700	4.1	2.4
0.5	almost no quenching		

of unimolecular radiationless decay and photodimerization, respectively.

$$1/\tau = k_d + k_r[M] \quad (1)$$

The lifetime of the reacting excited state for different maleimide concentrations was determined by biacetyl quenching of the dimerization.

Degassed acetonitrile solutions, containing  $1.0-10 \times 10^{-3} M$  maleimide and various concentrations of biacetyl, were irradiated simultaneously with 313 nm UV light. Relative quantum yields of disappearance of maleimide were determined by UV analysis. A linear Stern-Volmer plots obtained indicate that the photodimerization most probably occurs from one excited state at these low concentrations. This must be the triplet excited state since biacetyl is the triplet quencher and this proposition is supported by the lifetimes determined by the Stern-Volmer eq. (2).

$$\Phi_0/\Phi = 1 + k_q\tau[Q] \quad (2)$$

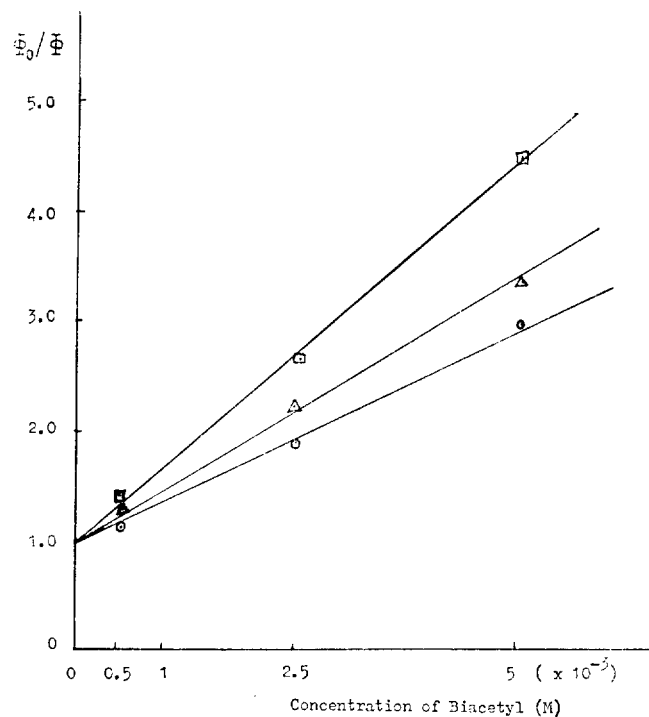
Representative Stern-Volmer plots for the quenching of the dimerization at different concentrations of maleimide are given in Figure 1. The slopes are tabulated in Table 3 and the values of the lifetime are calculated on the assumption that  $k_q$  equals the diffusion controlled rate constant,  $1.7 \times 10^{10} M^{-1} \text{sec}^{-1}$  in acetonitrile at 15°C, the temperature at which the reactions were carried out. The value of  $k_q$  was calculated on the basis of the eq. (3)

$$k_{\text{diff}} \doteq k_q = 8RT/3000\eta(\text{l/mole} \cdot \text{sec}) \quad (3)$$

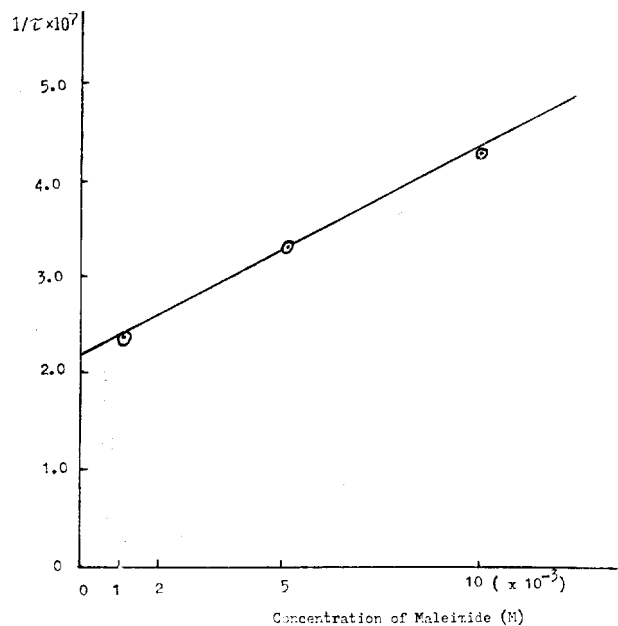
where  $\eta$  is the viscosity of the solvent.

A plot of  $1/\tau$  vs. maleimide concentration gave a good straight line (Figure 2) with a slope of  $2.0 \times 10^9 M^{-1} \text{sec}^{-1} (K_r)$  and an intercept at the ordinate of  $2.2 \times 10^7 \text{sec}^{-1} (K_d)$ .

**Characterization of the Photodimer.** Irradiation of the maleimide in the solution state resulted in the formation of solid photoproducts. The photoproduct was isolated by filtering followed by column chromatography. The structure of the photoproduct was characterized by spectroscopic methods and mass spectral analysis. It has a melting point of about 210°C. The EI mass spectrum of the photoproduct



**Figure 1.** Stern-Volmer plots for dimerization quenching of maleimide with biacetyl at different concentrations of maleimide: ○:  $1.0 \times 10^{-2}$  M, △:  $5.0 \times 10^{-3}$  M, □:  $1.0 \times 10^{-3}$  M.



**Figure 2.** A plot of  $1/\tau$  vs. maleimide concentrations.

**TABLE 4: Fragmentation Pattern of Mass Spectrum of Maleimide Photodimer**

<i>m/e</i>	Abundance	Fragment
194.0	93.7	$M^+$
151.0	100.0	$M^+ - \text{CONH}$
123.1	48.9	$M^+ - \text{C}_2\text{O}_2\text{NH}$
80.0	65.9	$M^+/2 - \text{OH}$
52.0	35.6	$\text{C}_4\text{H}_4$

shows the molecular ion peak at *m/e* 194 which is the molecular weight of maleimide dimer. The maleimide peak

at *m/e* 97 was relatively weak. The fragmentation pattern of photodimer is given in Table 4.

In the infrared spectra, maleimide shows a very broad peak at  $1700\text{ cm}^{-1}$  because carbonyl groups in maleimide are conjugated with a double bond. But the double bond is saturated in the photodimer, and carbonyl stretching bands appear at  $1770\text{ cm}^{-1}$  ( $\nu_{\text{as}}$ ) and  $1700\text{ cm}^{-1}$  ( $\nu_{\text{s}}$ ), the same frequencies at those of succinimide. A characteristic cyclobutane ring deformation band is also shown very strongly at  $830\text{ cm}^{-1}$  which is not observed in the maleimide spectra.

The  $^1\text{H}$  NMR spectra show only a singlet at 3.67 ppm which is similar to that of cyclobutane ring protons in the dimers of *N*-substituted maleimide (see Table 1). This suggests that the photodimer is a  $\text{C}_4$ -cyclodimerization product of maleimide formed through (2+2) addition as observed in *N*-substituted maleimides. The remainder of the spectra is consistent with the stereochemical configuration of cyclobutane ring in the photodimer of maleimide. Conclusive evidence for the stereochemistry of the photodimer will be obtained by x-ray studies.

### Conclusion

Maleimide undergoes  $2\pi + 2\pi$  cyclodimerization reaction on direct or sensitized excitation. The reaction occurs from the excited triplet state as determined by quenching and sensitization studies. The rate constant of cyclodimerization is found to be of the order of  $10^9\text{ M}^{-1}\text{ sec}^{-1}$  in the direct excitation.

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## Lithium Aluminum Hydride Reduction Studies of Rigid $\alpha$ -Oximino Ketones

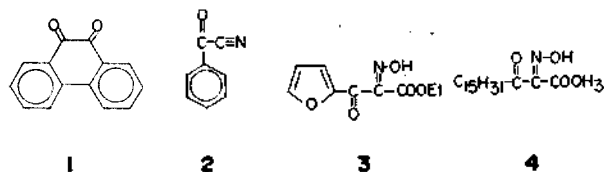
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Rigid  $\alpha$ -oximino ketones containing two functional groups such as 2-oximino-1-acenaphthenone and 2-oximino-1-indanone were synthesized and the simultaneous reduction of the two functional groups of  $\alpha$ -oximino ketones by  $\text{LiAlH}_4$  gave the corresponding amino alcohols, 2-amino-1-acenaphthenol and 2-amino-1-indanol. The yields of the reduction products of the  $\alpha$ -oximino ketones remarkably increased, as the increase of molar ratio of hydride used to the reactant. The use of 24 moles of  $\text{LiAlH}_4$  was found to afford the best result in the reduction of the rigid  $\alpha$ -oximino ketones to the corresponding amino alcohols. The yields was not affected by the variation of solvents such as ether, THF and diglyme.

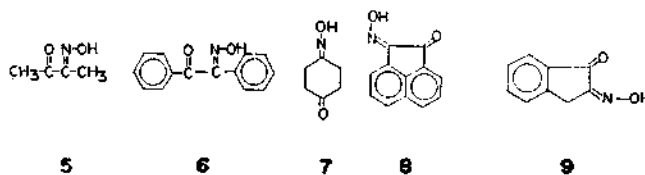
### Introduction

Lithium aluminum hydride is one of the most powerful hydride transfer reagents, which reduces a wide variety of functional groups such as ketones, esters and acids. Numerous reviews on reductions done with  $\text{LiAlH}_4$  have been reported.<sup>1</sup> However, Reductions of the compounds with the two adjacent reducible functional groups with  $\text{LiAlH}_4$  have not been studied systematically. Simultaneous reductions of 9,10-diketo-phenanthrene (1) and  $\alpha$ -cyano phenylketone (2) with  $\text{LiAlH}_4$  were reported to give high yields of the corresponding alcohols,<sup>2-4</sup> but ethyl 2-oximinofuroyl acetate (3)<sup>5</sup> and methyl 2-oximino-3-keto-octadecanoate (4)<sup>6</sup> reductions gave no reduction products.



The objective of this investigation is to deal with the  $\text{LiAlH}_4$  reductions of the oximino ketones such as biacetyl monooxime (5), benzil monooxime (6) 1,4-cyclohexanedione monooxime (7), 2-oximino-1-acenaphthenone (8) and 2-oximino-1-indanone (9). The cyclic  $\alpha$ -oximino ketones, 8 and 9 are structurally different from 5, 6 and 7.

The yields of reduction products of 5, 6 and 7 by 6-10



molar excess of  $\text{LiAlH}_4$  were moderate (20-40 %), but the cyclic  $\alpha$ -oximino ketones, 8 and 9 gave extremely low yield (0-10 %) under the same conditions. When 24 moles excess of  $\text{LiAlH}_4$  to reactant were employed to reduce 8 and 9, the yields were increased significantly ( $\approx 57$  %). The theoretical amount of  $\text{LiAlH}_4$  required to reduce 1 mole of  $\alpha$ -oximino ketones needs only 1.25 moles. Therefore, 24 moles used were exceedingly in excess of  $\text{LiAlH}_4$ , where in ordinary cases, the reduction yields have been known to be decreased due to the high reactivity of  $\text{LiAlH}_4$ .

The observed  $\text{LiAlH}_4$  reductions of the cyclic  $\alpha$ -oximino ketones such as 2-oximino-1-acenaphthenone (8) and 2-oximino-1-indanone (9) represent to the best of our knowledge the first demonstration of this action, although a number of other functional groups caused by  $\text{LiAlH}_4$  have been noted.<sup>1</sup>

### Results and Discussion

The oximino ketones, 5, 6, 7, 8 and 9 were made by the selective monooximation followed by the fractional crystallization of the mono and dioximes, and 2-oximino-1-indanone was prepared by the nitrosation of 1-indanone with