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$$[2,2,3,3] = (m/e\ 32)/0.239$$

$$[\text{scrambled isomers}] = x = (m/e\ 46) - [2,2,3,3]0.129 - [1,1,4,4]0.057 - [1,1,3,3]0.18$$

$$[1,1,3,3] = 2\{(m/e\ 47) - [2,2,3,3] - X0.18 - 0.028[1,1,4,4]\}$$

$$[1,1,4,4] = (m/e\ 45) - [1,1,3,3]0.568 - [2,2,3,3]0.136 - 0.247X$$

(8) Prepared by reduction of dimethyl succinate with lithium aluminum deuteride, conversion of the resulting diol to the dibromide (H_2SO_4/HBr), and reaction of the dibromide with Li metal (isotopic purity 98.5%).
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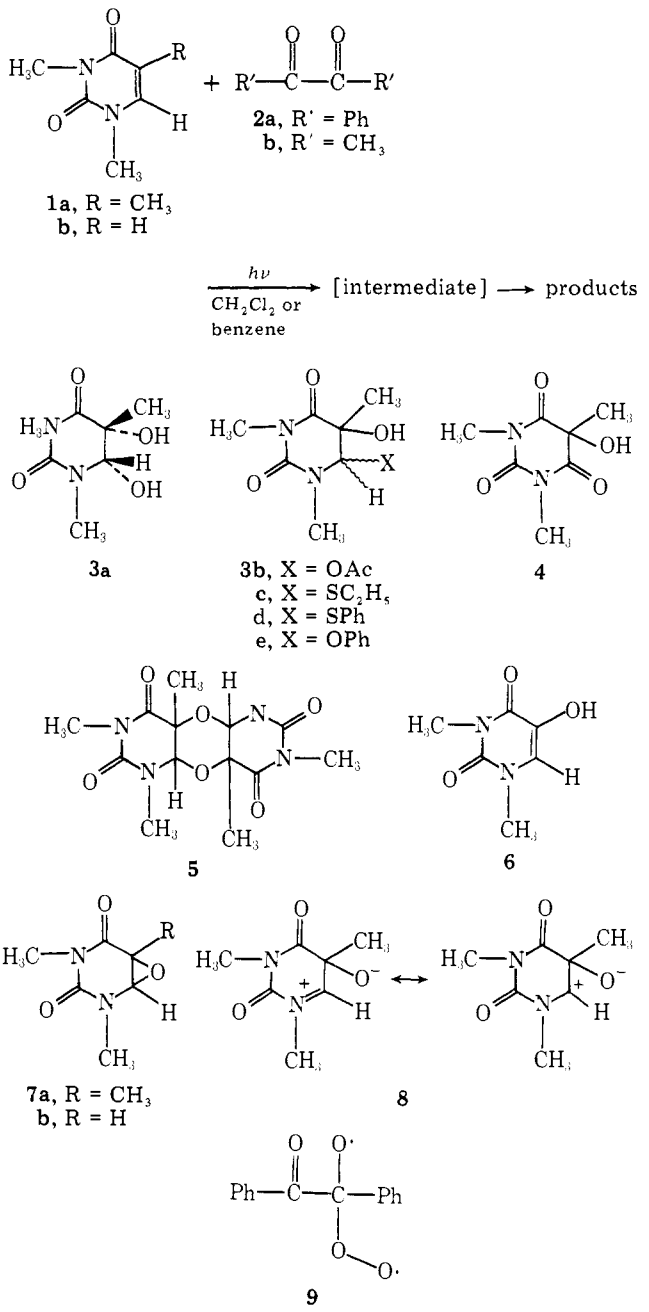
α-Diketone Sensitized Photooxidation of Pyrimidines

Sir:

Because of possible biological implications, the photosensitized oxidation of nucleic acids and their components has been extensively studied.[1] It was noted[1b] that in most cases the primary products of nucleic acid components are not well known because of the complexity of product mixtures and the tendency of initial products to undergo further reactions. In general, dye-sensitized photooxidation of simple olefins yields allyl hydroperoxides and/or dioxetanes which are believed to result from the interaction of the substrate molecules with singlet oxygen.[1b] However, Shimizu and Bartlett[2] have found that epoxides were produced as main products when α-diketones were used as sensitizers. They have shown that this photooxidation is quite different from that mediated by singlet oxygen and, also, from radical-chain autooxidations. This interesting finding prompted us to undertake a study of α-diketone sensitized oxidation of pyrimidines[3] because epoxidation of the nucleic acid components might be one of the initial oxidation reactions responsible for oxidative damage occurring in in vivo systems and because current findings in the study of organic epoxides[4] indicate their considerable importance in relation to biochemistry and environmental chemistry.[1b]

A CH_2Cl_2 solution of equimolar amounts (0.05 M) of 1,3-dimethylthymine (**1a**, Me_2Thy) and benzil (**2a**) was irradiated[5] for 1 h. The solvent was removed, and the products, separated by TLC on silica gel with eluent $CHCl_3$:CH_3CN (7:3), were found to be *cis*-Me_2Thy glycol (**3a**, 60%),[6] 5-methyl-5-hydroxybarbituric acid (**4**, 10%),[7] and (2,3),(6,5)-diMe_2Thy-1,4-dioxane (**5**, 3%).[8] No trans glycol could be detected. Using biacetyl (**2b**, 0.5 M) in place of **2a** and benzene as the solvent,[9] the reaction gave **3b** (**3a** 6-acetate, 85%)[9] in a regio- and stereospecific manner, and neither **3a** nor **5** was found. Postirradiation treatment of the former reaction mixture with acetic acid also gave **3b** (80%), but such a treatment of **3a** or **5** resulted in no reaction. Similar postirradiation treatment with thioethanol and thiophenol gave **3c** (90%)[10] and **3d** (90%),[11] respectively, whereas treatment with phenol yielded two isomers of **3e** (80%)[12] in approximately a 3:2 ratio.



These findings could be readily explained by assuming that pyrimidine epoxide (**7**) is the initial product. Its instability or reactivity may stem from the presence of a nitrogen atom α to the epoxide ring. The isolation of dihydropyrimidine derivatives (**3**) may result from the ring opening of an epoxide by various nucleophiles. The formation of **5** is particularly interesting because **5** is a dimeric product of **7** and is analogous to the commonly known formation of 1,4-dioxane from ethylene oxide.

Photosensitized oxidation of dimethyluracil (**1b**) with **2a** or **2b** was also studied and only 1,3-dimethylisobarbituric acid (**6**, 40%)[13] was obtained. Assuming that a corresponding epoxidation occurred, **6** is probably produced either directly from **7** by a hydride transfer[14] or through *cis*-uracil glycol which is known to convert readily to isobarbituric acid.[15]

Even though the stereochemistry of **3b–e** has not been determined, the stereospecific formation of a cis diol (**3a**) is in-

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consistent with the S_N2 mechanism through which products having the trans configuration result. The study of acid-catalyzed hydrolysis of 1-arylcyclohexene oxides has shown that the transition state leading to the cis diol has a higher degree of carbocationic character.[16] Furthermore, it has been demonstrated[17a] that the gauche conformer is more stable than the trans conformer in certain highly electronegatively substituted systems (gauche effect). Hence, it is reasonable to suggest that the reaction proceeds via an α-stabilized cationic intermediate **8** which may have a longer lifetime, thus allowing the attack of water from an energetically favorable direction to yield the cis diol. The favorable gauche interaction in this system is in agreement with the proposed mechanism for the stereospecific formation of *cis*-5-fluoro-6-methoxyuracil.[17e]

Regarding the photoepoxidation of simple olefins, a radical mechanism has been proposed and two possible pathways have been considered,[2] i.e., whether the initial step involves the interaction of the α-diketone with a double bond or with oxygen to yield the diradical **9**.[18] In methanolic solution, **2a** sensitized photooxidation of **1a** was found to result in a >95% recovery of **1a** and the complete oxidation of **2a**. This finding, along with those above, suggests that **9** may be the initial intermediate which reacts with pyrimidines to give **7** in an aprotic solvent. In methanol **9** is trapped by the solvent, thus precluding its reaction with the pyrimidine. However, the possibility that a mechanism may involve an ionic intermediate cannot be excluded because there have been such suggestions recently concerning the dye-sensitized photooxidation of pyrimidines[3c] or indoles.[19] Consequently, more detailed mechanistic study is being undertaken.

In short, the evidence indicates that pyrimidine epoxides may be formed as initial photooxidation products. It also shows that such intermediates are exceedingly susceptible to the attack of nucleophiles, yielding compounds corresponding to **3**, and that **3b–e** are readily converted to **3a**, resulting in the cleavage of the newly formed covalent bond. Furthermore, the nucleophilic attack of pyrimidine epoxides offers an alternative mechanism for the formation of protein–nucleic acid cross-linkings, which command current interest[20,21] and should be relevant to the study of aging, carcinogenesis, and mutagenesis.

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(6) **3a** was identified by comparison with an authentic sample, prepared from **1a** according to the method of S. Iida and H. Hayatsu, *Biochem. Biophys. Acta*, **228**, 1 (1971), for Thy glycol.

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(8) Characteristics of **5**: *m/e* 340 (M^+); NMR ($CDCl_3$, Me_4Si): δ 1.39 (6 H, s), 3.19 (6 H, s), 3.23 (6 H, s), and 4.59 (2 H, s); mp >230 °C.

(9) In contrast to **2a**, **2b** was consumed rapidly. Irradiation in CH_2Cl_2 gave a lower yield (40%) of **3b** while another product was formed in a greater yield. **3b** is readily converted quantitatively to **3a** in the presence of a catalytic amount of silica gel at room temperature. Characteristic of **3b**: mp 122 °C; *m/e* 230 (M^+); NMR ($CDCl_3$, Me_4Si): δ 1.48 (3 H, s), 2.07 (3 H, s), 3.12 (3 H, s), 3.24 (3 H, s), 5.88 (1 H, s), and 7.26 (1 H, bd).

(10) **3c** is a viscous liquid: *m/e* 132 (M^+); NMR ($CDCl_3$): 1.24 (3 H, t, J = 7.0 Hz), 1.50 (3 H, s), 2.67 (2 H, q, J = 7.0 Hz), 3.13 (3 H, s), 3.15 (3 H, s), 4.21 (1 H, s), and 5.96 (1 H, bd).

(11) **3d** has mp 136 °C; *m/e* 280 (M^+); NMR ($CDCl_3$): 1.48 (3 H, s), 2.85 (3 H, s), 3.04 (3 H, s), 3.70 (1 H, bd), 4.45 (1 H, s), and 7.29 (5 H, m).

(12) One isomer of **3e** has mp 204 °C; *m/e* 264 (M^+); NMR (CD_3COCD_3–$CDCl_3$, Me_4Si): δ 1.56 (3 H, s), 2.96 (3 H, s), 3.17 (3 H, s), 4.22 (1 H, s), 6.80 (5 H, m), and 8.18 (1 H, bd). The other is a viscous oil with *m/e* 264 (M^+); NMR ($CDCl_3$): δ 1.68 (3 H, s), 3.03 (3 H, s), 3.27 (3 H, s), 4.68 (1 H, s), 5.00 (1 H, bd), and 6.86 (5 H, m).

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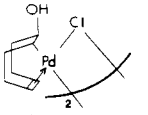
Stereochemistry of the Hydroxypalladation of Ethylene. Evidence for Trans Addition in the Wacker Process

Sir:

The hydroxypalladation step in the conversion of ethylene to acetaldehyde has been proposed,[1] on the basis of kinetic studies, to proceed with cis stereochemistry. Thus, the trans addition of methanol and palladium to chelating diolefins[2,3] was considered to be anomalous[4–8] since the chelating diolefin could not undergo a 90° rotation readily from a position perpendicular to the square plane of the complex into a position in which one of the olefin pair is coplanar with the square plane of the complex and thus adjacent to the alkoxyl function, a position necessary for cis attack. However, the trans stereochemistry of methoxypalladation of monoolefins, *cis*- and *trans*-2-butene, has been demonstrated by intercepting the β-methoxyalkylpalladium complex with carbon monoxide.[9] The presence of carbon monoxide in this reaction apparently does not alter the stereochemical course, since a β-methoxyalkylpalladium complex, isolated at low temperature, has been shown[10] to have the trans geometry.

The stereochemistry of the methoxypalladation of diolefins can no longer be considered anomalous; the presence of carbon monoxide in these reactions does not alter the stereochemical course of the reaction. The stereochemistry observed in methanol, however, does not necessarily include the reaction in aqueous media, particularly under the conditions of the Wacker process. We had demonstrated[11] that the hydroxypalladation of 1,5-cyclooctadiene in water–acetone produced the trans σ-bonded hydroxy-enyl complex **1.** In order to con-



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firm this stereochemistry, we undertook a hydroxypalladation of a monoolefin with the anticipation that the Wacker intermediate could be trapped with carbon monoxide.

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