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PHOTOCHEMICAL FRAGMENTATION OF PHOTOTOXIC 2-ARYLQUINOLINEMETHANOLS

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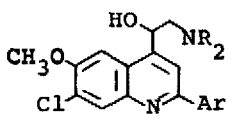
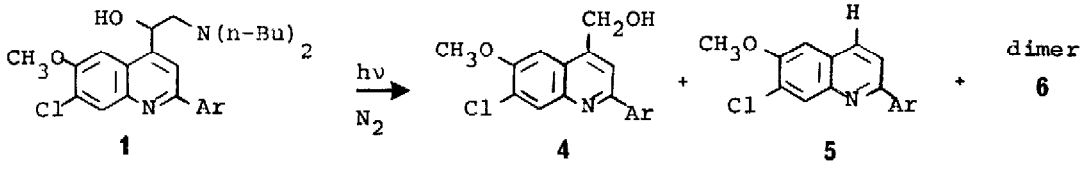
A surprisingly large number of synthetic 2-aryl-4-quinolinemethanols, such as 1-3, have shown significant activity as antimalarial compounds.[1] Unfortunately, their medicinal use has been precluded by their accompanying phototoxicity.[2] Although it has been suggested that the phototoxicity results from a mechanism involving photosensitization of oxygen,[3] the intermediacy of singlet oxygen seems unlikely in light of the known tendency of tertiary aliphatic amines to efficiently quench singlet oxygen.[4] Consequently, we have sought to determine whether the electronically excited states of the phototoxic 1-3 are chemically active even in the absence of oxygen. In all cases, we observed an efficient characteristic photochemical pathway of reaction.



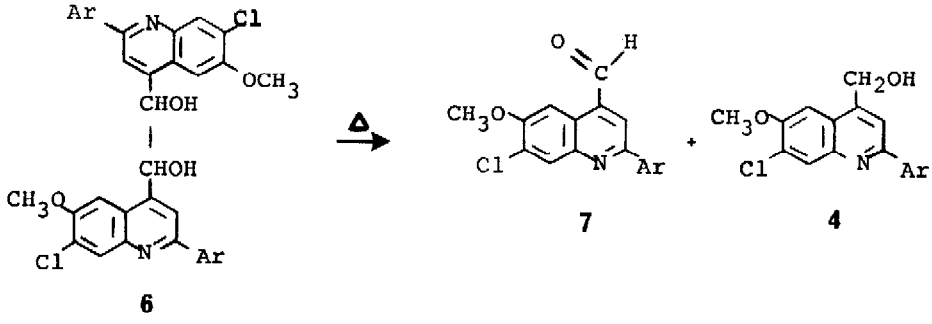
1, R = n-Butyl
2, R = Ethyl
3, R = n-Hexyl

Ar = p-CH_3O-C_6H_4

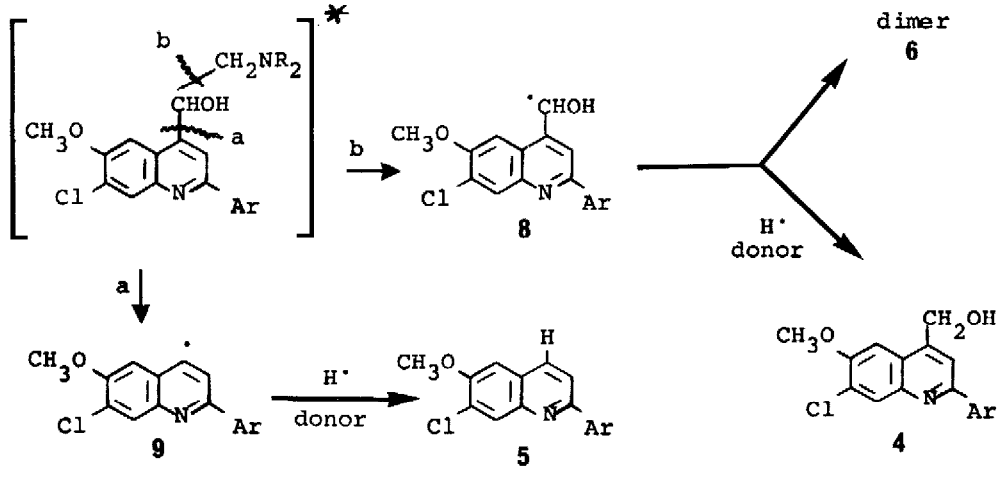
Compounds 1-3 were prepared by the synthetic route of Gillespie.[1] Irradiation of 1 (450 W Hanovia medium-pressure mercury lamp, pyrex filter, isopropyl alcohol solvent) produced two major products, separable by silica gel chromatography. In addition, a small amount of dimer 6 was produced, which precipitated from the solution as it was formed.



The structures of 4 and 5 were established by spectral analysis (ir and nmr) and independent synthesis.[5] The structure of dimer 6 was clarified by mass spectroscopy and its pyrolysis to form equal amounts of alcohol 4 and aldehyde 7, a common type of fragmentation with aromatic pinacols.[6]

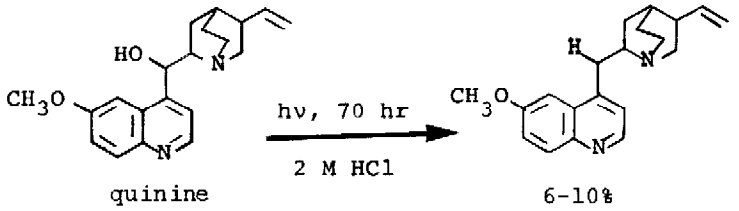


Photolysis of 1 in methanol gave evidence for a common precursor to 4 and 6. In this solvent (a poor hydrogen atom donor) only minor amounts of alcohol 4 were obtained, but the yield of dimer 6 was correspondingly increased. A mechanism which accounts for these observations is shown below:



Formation of the dimer from 8 is thus competitive with hydrogen atom abstraction to produce 4. In the presence of a good hydrogen atom donor (isopropyl alcohol), little dimer is produced. Conversely, a poor hydrogen donor (methanol) allows dimerization to predominate. Interestingly, the higher reactivity (lower stability) of intermediate 9 causes it to abstract a hydrogen from even a poor donor before dimerization can occur.

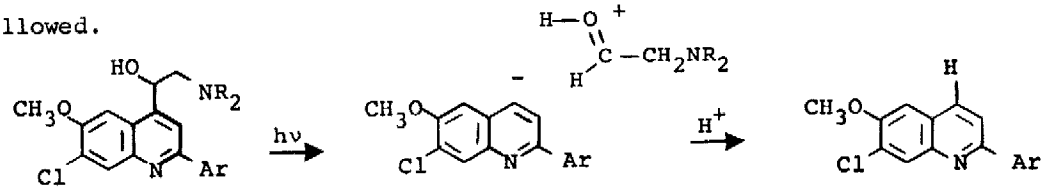
The fragmentation processes observed are rather unique. The most closely related photochemical study is Stenberg's research on the photochemical behavior of quinine and its diastereomers.[7] In sharp contrast with the present study, these compounds are quite unreactive photochemically, undergoing a slow photochemical reaction only in strongly acidic medium, and by an apparent ionic pathway.



quinine 6-10%

The product obtained results from a cleavage of the C-O bond, in contrast to the C-C bond cleavage observed here.

The surprising formation of products from homolytic cleavage suggests unexpected stability of intermediates 8 and 9. The ability of "path a cleavage" to compete with "path b cleavage" is even more surprising, since it can only be formed by breaking an sp^2-sp^3 bond. A mechanism involving heterolytic cleavage is an attractive alternative, but this type of fragmentation should be greatly favored by photolysis in the more polar methanol solvent. Our failure to observe enhancement of this pathway is indirect evidence that this pathway is not followed.



The photolysis of 2 or 3 proceeds quite similarly to the photolysis of 1, yielding 4,5, and 6 as products. The most phototoxic compound, 2, reacts most efficiently, undergoing complete reaction of 200 mg in only 30 min of photolysis. The least phototoxic compound, 3, is also the most photochemically stable.

The facile photochemical reaction of compounds 1-3 suggests a viable alternative to the photosensitization mechanism of phototoxicity. In vivo radical reactions could lead to tissue damage by reactions with proteins or nucleic acids. We are continuing our studies to provide further information about the chemical mechanism of phototoxicity.

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