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The Investigation of Photochemical Reactions of Phototoxic Antimalarial Compounds

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The goal of this research is to provide information that will lead to the development of new non-phototoxic antimalarial compounds. The goal was approached by first learning the chemical mechanism of phototoxicity of six representative compounds **1a-f**: α-[(diethyl-, -dihexyl-, and -dioctyl-aminomethyl)]-2-(3′, 4′ -dichlorophenyl)-6-methoxy-4-quinolinemethanol (**1a**, **1b**, and **1c**) and α-[(diethyl-, -dibutyl-, and -dihexyl -aminomethyl)]-2-(4′ -methoxyphenyl -6-methoxy-7-chloro-4-quinolinemethanol (**1d**, **1e**, and **1f**). The photochemical reaction of these compounds was investigated in 2-propanol. Similar photochemical fragmentation reactions occurred in all compounds. Five products (**15**~**19**), formed via cleavage of the whole side chain (bond "α" cleavage) and cleavage of bond between α-carbon and hydroxy carbon (bond "β" cleavage), were isolated and identified; 2-(3′, 4′ -dichloro-, phenyl)-6-methoxyquinoline (**15**), 2-(3′, 4′ -dichlorophenyl)-4-hydroxymethyl-6-methoxyquinoline (**16**), 2-(3′, 4′ -dichlorophenyl)-6-methoxyquinoline-4-carboxaldehyde (**17**), 2-(3′, 4′ -dichlorophenyl)-4-(α,β-dihydroxy-β-methyl-propyl)-6-methoxyquinoline (**18**), and the pinacol-type dimer of **16** (**19**). A radical mechanism was proposed for the formation of **15**~**19**. Quantum yields of the photochemical reaction of **1a-f** were measured to determine if the efficiency of the reaction parallels the degree of phototoxicity of **1a-f**. A good qualitative correlation was observed.

Fluorescence study of **1a-d**, 2-(3′, 4′ -dichlorophenyl)-4-ethyl-6-methoxyquinoline 2-(3′, 4′ -dichlorophenyl)-4-(a-hydroxyethyl)-6-methoxyquinoline, and 2-(4′ -methoxyphenyl)-4-(α-hydroxyethyl)-6-methoxy-7-chloroquinoline was performed to investigate whether intramolecular exciplex formation between an aliphatic amine group and quinoline ring could intervene in the photochemistry of 2-arylquinolinemethanols. Significant intramolecular fluorescence quenching by the aliphatic amine group of **1a-d** was noticed.

Sensitization irradiations of **1a** with triplet sensitizers failed to produce **16**~**19**, producing only **15** in low yield. The reaction of **1a-f** was partially quenched by oxygen. The singlet excited state and an intramole-

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cular exciplex of 2-arylquinolinemethanols were postulated to be reactive states for their photochemical reactions.

Photochemical reactions of cinchonidine (**33a**), quinine (**33b**), cinchonine (**33c**), quinidine (**22d**), and mefloquine (**50**) were investigated. 5-Vinylquinuclidine-2-carboxaldehyde (**34**) was isolated and identified as a major product in the reaction of **33a-d**. The formation of **34** was rationalized by a charge transfer mechanism. Bond "β" cleavage was blocked by the bicyclic amine group, quinuclidine of **33a-d**. A different photochemical reaction was observed in the photolysis of **50** from those of **1a-f** and **33a-d**, and 2,8 bis(trifluoromethyl)-4-carbomethoxyquinoline was isolated as the major photoproduct in methanol.

Finally, structural changes to increase charge transfer character in the intramolecular exciplex and to increase the efficiency of intersystem crossing were suggested as ways to stop or diminish the phototoxicity of 2-arylquinolinemethanols.