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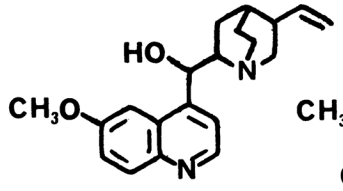
PHOTOCHEMICAL REACTIVITY OF MEFLOQUINE, A NEW SYNTHETIC ANTIMALARIAL

Gary A. EPLING* and Ung Chan YOON

Department of Chemistry
University of Connecticut
Storrs, CT 06268

Summary: The photochemistry of mefloquine, an experimental antimalarial drug, has been examined with an eye towards understanding its comparatively low phototoxicity.

The growing resistance of Plasmodia to currently-used antimalarials has spurred interest in the synthesis of possible replacement drugs to which resistance has not developed. The long-recognized antimalarial activity of quinine, 1, led to the development of analogs such as 2 which, as a class, have shown excellent activity in preliminary screening. Unfortunately, an accompanying side effect of phototoxicity (light-induced skin damage) has precluded the clinical use of such compounds.[1] Ohnmacht, Patel, and Lutz[2] prepared "mefloquine", 3, during an active program of synthesis of compounds similar to 2 in the hope that it would retain the antimalarial activity of 2 but not exhibit the phototoxic side effect. Preliminary testing showed the compound to have "relatively low" phototoxicity,[2] and clinical screening tests have been promising.[3]



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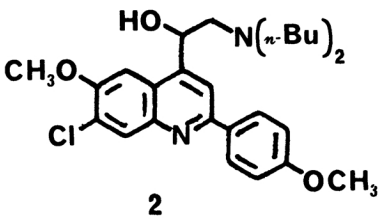

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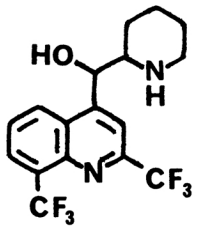

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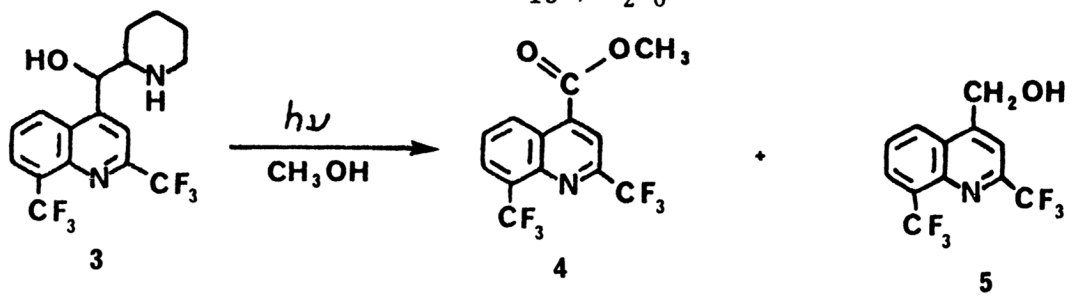
We have previously observed[4] that the phototoxic quinolinemethanols such as 2 undergo an efficient photofragmentation reaction which leads to the formation of free radicals, the apparent cause of the *in vivo* phototoxicity.[5] In contrast, the photocleavage[6] of the non-phototoxic quinine is much slower, and the relatively sluggish photochemical reactivity is consistent with its weak phototoxicity. We were intrigued by the low phototoxicity of 3, and have studied its photochemistry to attempt to explain the low phototoxicity on a molecular basis. We now report a number of differences between its behavior and that of the phototoxic compounds exemplified by 2.

A solution containing 100 mg of mefloquine, 3, (free base) in 1400 mL of methanol stirred with a stream of nitrogen was irradiated through a pyrex filter sleeve in an immersion well apparatus for 2.5 hr using a Hanovia 450W medium-pressure mercury lamp. The reaction was monitored by tlc (Eastman Chromagram sheets, using 5% CH_3OH/CH_2Cl_2 and 40% CH_2Cl_2/hexane as eluents), the reaction being halted when only ca. 10% of the starting material remained. Removal of the solvent under reduced pressure yielded 75 mg of a solid which was chromatographed on a column containing 10 g of silica gel (Davison, Grade 62). Elution with 5% CH_2Cl_2/hexane afforded 43 mg (55% yield) of 4-carbomethoxy-2,8-bis(trifluoromethyl)quinoline, 4, as the major product, mp 81-82.5. The nmr, ir, and mass spectra were consistent with the assigned structure. High resolution m.s.: calculated for $C_{13}H_7NO_2F_6$ 323.03809; found, 323.0378.



3 4 5

In addition to 4 there was formed in barely detectible amounts (ca. 5%) alcohol 5, and about 5% of a third product which was too unstable to fully characterize, though the mass spectrum suggested it also was a fragmentation product.

The structure of 5 was confirmed by its preparation from a $NaBH_4$ reduction of 40 mg of 4, using 15 mg $NaBH_4$ in 5 mL methanol to give 36 mg (95%) of 4-hydroxymethyl-2,8-bis(trifluoromethyl)quinoline, 5, mp 124.5-126. The nmr, ir, and mass spectra, as well as elemental analysis[7] were all consistent with the assigned structure.

The low yield of 5 contrasted with the behavior of compounds such as 2, so it was necessary to establish that it was not being destroyed during the irradiation. Photolysis of 3.5 mg of 5 in 50 mL of methanol under the same conditions used before showed that it was quite inert, and the irradiation was continued for 10 hr before a high (ca. 70%) conversion was attained. In this irradiation several products were observed, none of which were found in the photolysate of 3, showing that secondary photolysis of 5 was not the source of its low yield.

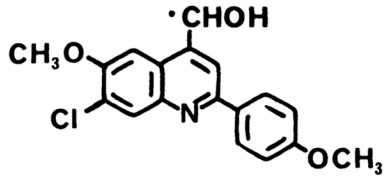
We can summarize three major factors which seem to be responsible for the decreased phototoxicity of 3:

(1) The phototoxic compounds such as 2 have strong absorption in what is called the "UVA" region (>320 nm) the light which seems responsible for causing phototoxicity in most cases.[8] Instead of having a λ_{max} at 350 nm with ε of 10^4 (which precedes a significant tail up to 375 nm) 3 has a weak absorption, the band at λ_{max} 318 ($\varepsilon = 3 \times 10^3$) dropping off sharply so that virtually no absorption is seen beyond 350.

(2) The efficiency of the photochemical reaction of 3 is substantially lower than that of 2, the comparative quantum yields for reaction being 0.05 for 2 and 0.005 for 3.

(3) The type of cleavage pathway followed is very different. The products formed in the irradiation of 2 are consistent with radical 6 as a precursor, as is the formation of 5 from 7. However, 5 is a very minor product. The pathway to 4 is probably much more complex, and does not appear to involve free radicals. While the irradiation of 2 in the presence of the thiol-containing tripeptide glutathione gave rise to an almost quantitative yield of

the dimeric oxidized disulfide (presumably by abstraction of a hydrogen atom from the sulfur and coupling of the resulting sulfide radicals) the irradiation of 3 in the presence of glutathione caused very little of this product to be formed. Though the mechanism of the reaction of 3 remains to be clarified, its reluctance to give reactive free radicals is likely another reason for its low phototoxicity.



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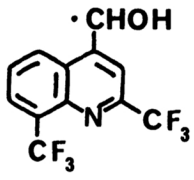

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