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PHOTOLYSIS OF CINCHONA ALKALOIDS. PHOTOCHEMICAL DEGRADATION TO 5-VINYLQUINUCLIDINE-2-CARBOXALDEHYDE, A PRECURSOR TO SYNTHETIC ANTIMALARIALS

Gary A. Epling* and Ung Chan Yoon
Department of Chemistry, Fordham University, Bronx, N.Y. 10458

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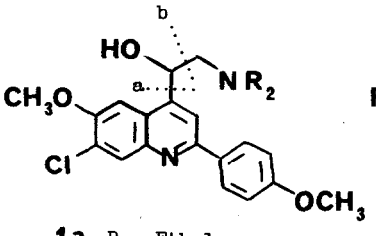
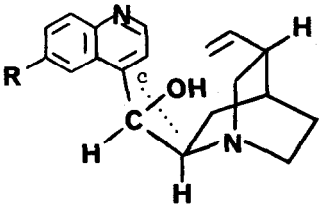
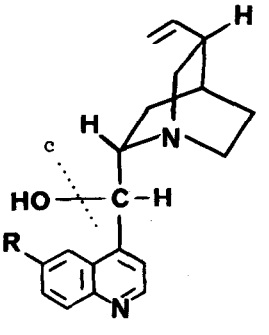
We have previously reported[1] that the irradiation of the phototoxic quinolinemethanol antimalarials 1a-c leads to a rapid photochemical fragmentation in which products are formed by cleavage of bonds "a" and "b". In contrast, Stenberg[2] has observed that the photolysis of the Cinchona alkaloids 2a-d leads to the formation of the corresponding "deoxy" compounds, the products of bond "c" cleavage. Although the Cinchona alkaloids differ structurally in two important ways (no 2-phenyl substituent and a bicyclic quinuclidine side chain) the totally different photochemical reactivity was surprising. However, we noted that Stenberg's



1a, R = Ethyl
b, R = n-Butyl
c, R = n-Hexyl



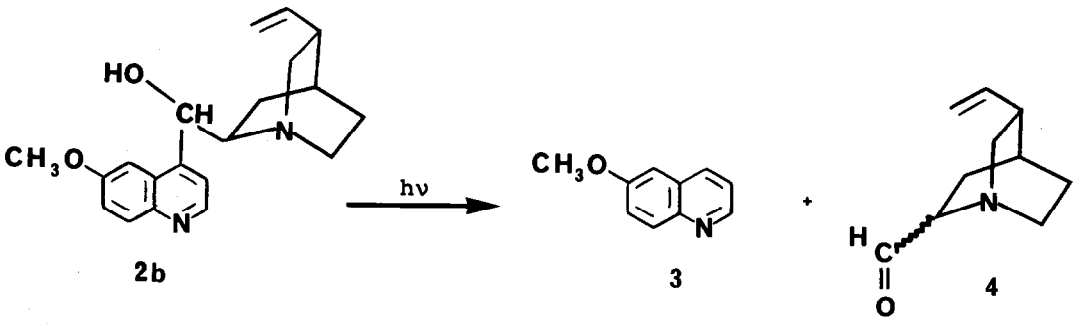
2a, Cinchonine, R = H
b, Quinidine, R = OCH_3



2c, Cinchonidine, R = H
d, Quinine, R = OCH_3

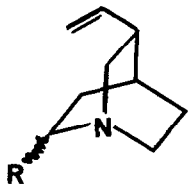
photolyses were performed in 2M HCl, and thus presumably go via a mechanism involving the triprotonated alkaloids. Since we had observed bond "a" and "b" cleavage of la-c under neutral conditions, we have repeated Stenberg's study of quinine, quinidine, cinchonine, and cinchonidine, but photolyzed in a neutral solvent. In contrast to their reported behavior in acid, under neutral conditions 2a-d react faster, and give photoproducts analogous to those of the synthetic antimalarials la-c.

Photolysis of all four alkaloids under neutral conditions (methanol solvent, Hanovia medium-pressure mercury lamp, vycor filter, nitrogen purging) led mainly to the formation of two fragmentation products. Quinidine (2b), for example, gave 6-methoxyquinoline (3) and 5-vinylquinuclidine-2-carboxaldehyde (4). The structure of 3 was confirmed by the comparison of its nmr spectrum and the mp of its picrate with those of authentic 3. The

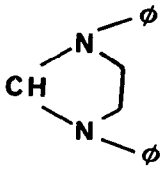


2b 3 4

structure of 4 was established by comparison of its 100 MHz nmr spectrum and its infrared spectrum with those of authentic 4.[3,4] The structure of 4 was further confirmed by the preparation of several derivatives. Reaction of 4 with sodium borohydride led to alcohol 5 (ir: 3320 cm^{-1}, -OH); treatment of 4 with 1,2-dianilinoethane gave the imidazolidine derivative, 6 (nmr: δ 6.5-8.0, 10 H mult, phenyl); and oxidation with Ag_2O followed by esterification in ethanol gave the ethyl ester, 7 (ir: 1730 cm^{-1}, C=O; lit[4] 1732 cm^{-1}). Typically, a photolysis of 2.0 g of 2b gave 4 in 50-60% yield (determined by nmr--comparative integration of the aldehyde proton with that of 3,4-dichlorobenzaldehyde, added after photolysis to serve as an internal standard), though isolation by chromatography on silica gel gave only about



5, R = CH_2OH

6, R = 

7, R = CO_2Et

half this amount due to the lability of 4.[4] It is likely that 4 equilibrates to a thermodynamic mixture of epimers in all cases, since the spectral properties of the product are identical from the photolysis of 2a, 2b, 2c, and 2d--though the initial stereochemistry at carbon-2 differs from case to case.[5]

The photolysis of the other three cinchona alkaloids proceeds quite like that of 2b, yielding products of bond "a" cleavage as the major photochemical pathway. However, the rate of reaction of cinchonidine and quinidine was somewhat faster than the reaction of quinine and cinchonine, and the best yields for 4 were obtained with the former two compounds.

This simple and facile one-step method for preparation of 4 may be valuable, since this compound has been treated with a variety of aryllithium reagents to produce compounds which have antimalarial and antiarrhythmic activity.[6] Compound 4 was previously available only through the elegant, but somewhat lengthy, total synthesis of Uskokovic and Grethe.[4,7]

Although the major photochemical pathway led to the formation of 3 and 4 by cleavage of bond "a", there were small amounts of products of bond "b" cleavage as well. Hence, the photochemical reactivity of quinine and the other alkaloids closely parallels that of the synthetic antimalarials 1a-c.[1] The different reaction of 2a-d in acid solution[2] suggests that protonation blocks reaction via pathways that lead to bond "a" and "b" cleavage. We could detect no "deoxy" products (bond "c" cleavage) from photolysis under neutral conditions, although we prepared the authentic materials for tlc and spectral comparison. Thus, the only major difference in the photochemical reactivity of 1a-c and 2a-d is that the quantum

efficiency of the reaction of the natural alkaloids is quite lower than that of the synthetic phenyl-substituted compounds. Interestingly, the phototoxicity which plagues the use of compounds such as 1a-c[8] is not generally a problem associated with the medicinal use of quinine or quinidine. We are continuing to investigate whether the facile photochemical reactivity of 1 is the underlying cause of its phototoxicity in mammals.

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