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LASER PHOTOCHEMISTRY: THE WAVELENGTH DEPENDENT OXIDATIVE PHOTODEGRADATION OF VITAMIN K ANALOGS

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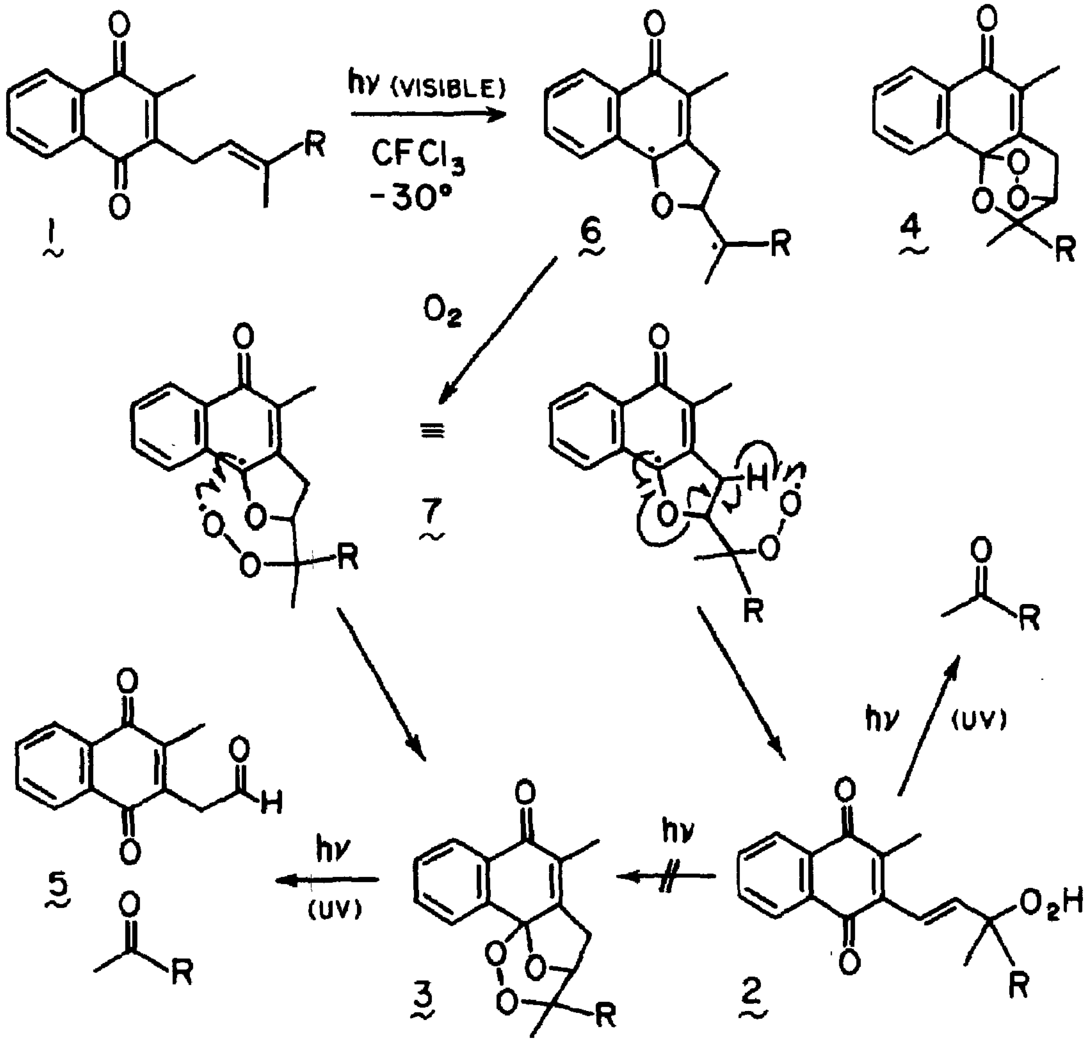
Menaquinone-1 and phylloquinone have been observed to form stable trioxanes when irradiated with visible light under aerobic conditions. The menaquinone-1 peroxide derivative has been shown to be extremely photolabile to ultraviolet light.

The photoinactivation of oxidative and coupled phosphorylation in Mycobacterium phlei has been traced to the photooxidation of vitamin K (menaquinone-9, MK-9, 1a).[1] These observations have prompted Snyder and Rapoport to investigate the photooxidation of phylloquinone and menaquinones in vitro.[2] Ultraviolet irradiation (G.E. blacklights F15T8-BLB) of these quinones in an oxygen atmosphere afforded the allylic hydroperoxides related to 2 as minor products, along with the methyl ketones arising from oxidative cleavage of the β,γ-double bond in the side chain as the major product (Scheme I). The fate of the naphthoquinone moeity could not be determined. These oxidation products were shown not to arise from singlet oxygen as only the β,γ-double bond was oxidized and sensitized oxidations did not produce the same products. Based on these findings, an intermediate complex between the excited carbonyl, the β,γ-double bond, and molecular oxygen was proposed. The possibility existed that this complex was in fact a 1,2,4-trioxane similar to the intramolecular example observed by Creed, Werbin and Strom[3] and to the intermolecular examples observed in our work.[4] This speculation has now been confirmed by the following study of the photooxidation of menaquinone-1 (MK-1, 1b).[5]

Irradiation of MK-1 (1b) with a blue line of an argon ion laser (457.9 nm, 1.7-2.0 watts) in $CFCl_3$ at -30° under a high pressure oxygen atmosphere (150 psi) affords two products both of which decomposed significantly upon silica gel chromatography: the known hydroperoxide 2b[2] (34% isolated) and the trioxane 3b (31% isolated) which had: m.p. 164-165°C; M^+ (m/e) = 272; IR 1650 cm^{-1}; nmr (δ, $CDCl_3$) 8.00 ppm (1H, complex), 7.58 (3H, complex), 4.39 (1H, dd, J = 1 and 6 Hz), 3.30-2.60 (2H, complex), 1.98 (3H, t, J = 1 Hz), 1.76 (3H, s), and 1.12 (3H, s). That this trioxane is the [3.2.1] isomer 3b and not the [2.2.2] isomer 4b is indicated by the formation of a dihydronaphthofuran upon reduction with $NaBH_4$[3] as well as the many examples of trioxanes in which the peroxide linkage is introduced at the more highly substituted olefinic carbon atom.[4]

The thermal stability of 3b is quite high as it can be recovered unchanged after 4 days at 50°C in chloroform, and is only slowly decomposed at higher temperatures in the same solvent. Quantitative



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a $-CH_2[CH_2CH{=}C(CH_3)CH_2]_8H$

b $-CH_3$

c $-CH_2[CH_2CH_2CH(CH_3)CH_2]_3H$

Scheme I

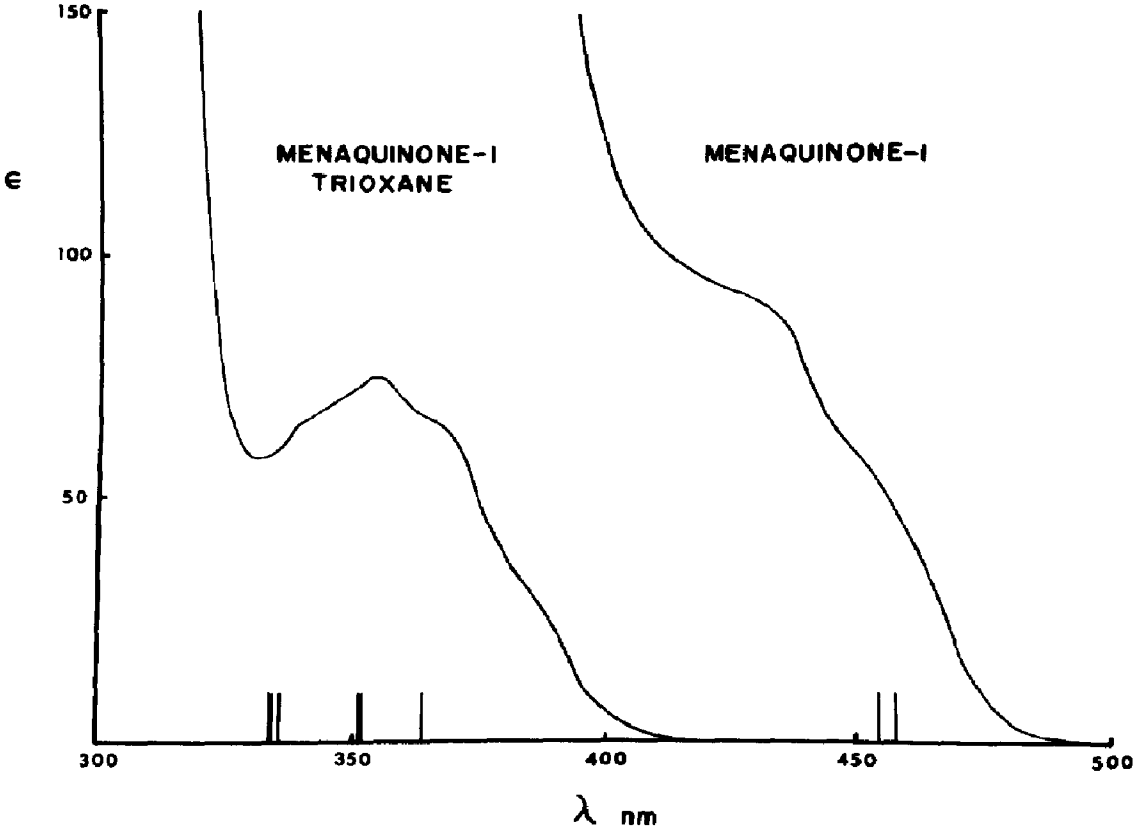
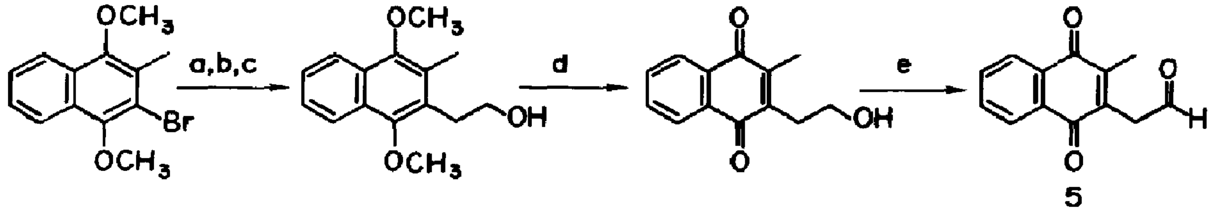


Figure 1. Long wavelength absorption edge for menaquinone-1 (1b) and menaquinone-1 trioxane (3b). Relevant argon laser lines are indicated on the abscissa.

formation of acetone requires 36 hours at 120°C.[6] In contrast 3b is extremely photolabile. Since the wavelengths of light used to produce 3b (457.9 or 454.5 nm) are not absorbed by 3b (Figure 1), it accumulates under these conditions. However, if 3b is irradiated with the ultraviolet output of an argon ion laser (363.8, 351.4, 351.1, 335.8, 334.5, 333.6 nm lines at 2.8 watts) (Figure 1), it is rapidly cleaved to acetone (89%) and a very photolabile quinone aldehyde 5 (24%). The acetone was isolated as its 2,4-DNP and the structure of 5 was confirmed by synthesis (Scheme II). Irradiation of the hydroperoxide 2b under the same conditions afforded acetone (90%) but the formation of 5 could not be established in this case.



Scheme II

a) n-BuLi, THF, -78°; b) $\overset{O}{CH_2\text{——}CH_2}$, THF; c) H_2O (90%a-c); d) AgO, HNO_3, dioxane, RT (90%); e) pyridinium chlorochromate, NaOAc, CH_2Cl_2, RT (95%)

Also the transformation of the hydroperoxide 2b to the trioxane 3b upon irradiation with visible or ultraviolet light, which had been suggested earlier, could not be observed.[4] Finally, irradiation of phylloquinone (1c) proceeds in a similar fashion to yield two trioxanes which appear to differ in the configuration of the prenyl chain (-R).

The formation of 2b and 3b is most easily rationalized as the trapping by oxygen of a quinone-olefin exciplex or 1,4-preoxetane biradical such as 6b. In related trapping work a stepwise process seems to obtain.[7] Thus, the initial oxygen trapping product might be the hydroperoxy biradical 7b. This species might either collapse to the trioxane 3b or undergo hydrogen abstraction to afford the hydroperoxide 2b. The mechanism(s) by which the peroxides undergo photodecomposition is not clear.[8]

Finally, the facile formation of these trioxanes with visible light and their stability implies that they may well be produced and accumulate in appropriate biological systems.

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