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CHEMICAL OXYGENATION OF VITAMIN D_3

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Recently considerable attention has been directed toward the generation and reactions of the first excited state of molecular oxygen, singlet oxygen, $O_2(\Delta^1)^3$. Singlet oxygen is known to be a powerful biochemical oxidant[4,5]. Inglett[6] has recently found that the biological antioxidant α-tocopherol undergoes oxidation with singlet oxygen in solution to yield a variety of products. Our attention was drawn to the potential reaction of $O_2(\Delta^1)$ with the unsaturated portion of vitamin D_3 (1).

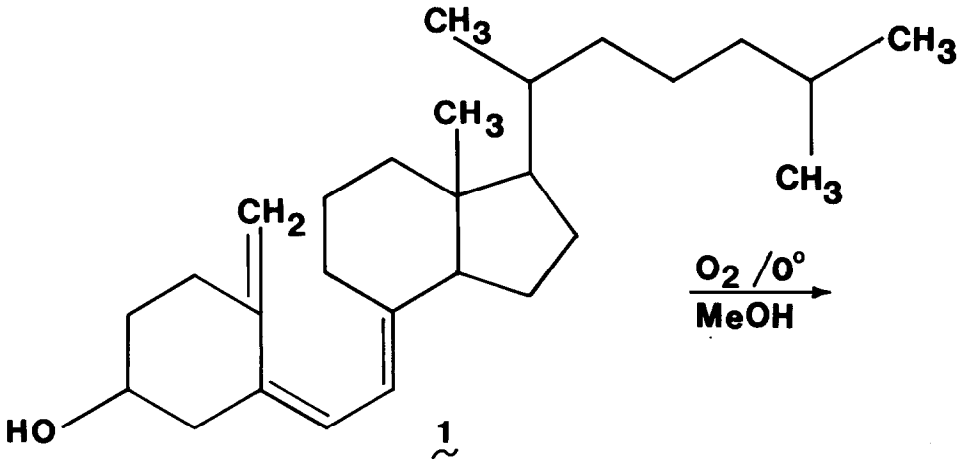
Vitamin D_3 has been found[7] to be stable in oil in the presence of oxygen for many months at 38°, however its lability when exposed to singlet oxygen is unknown. Singlet oxygen is known to react with dienoid systems in a 4+2 cycloaddition fashion[8] to yield dioxolane products, therefore Vitamin D_3 with its trienic functionality presented itself as an admirable singlet oxygen substrate. When vitamin D_3 was treated in a methanol solution at 0-5° with a ten-fold molar excess of singlet oxygen generated *in situ* from sodium hypochlorite-hydrogen peroxide, we were most surprised to find that isolation and purification at 5° led to none of the expected dioxolane products, but rather to product **2** which represented the incorporation of two molecules of methoxide. In separate experiments when D_3 was treated singularly with hypochlorite, hydrogen peroxide or sodium methoxide under the same reaction conditions none of the dimethoxyl product **2** was isolated. Subsequent runs demonstrated that when the D_3-singlet oxygen mixture was quenched with sodium borohydride prior to workup the yield of **2** was increased from 14 to 38%. This enhanced yield is undoubtedly due to reduction of hydroperoxide impurities in the reaction mixture which if not reduced lead to oxidation of the D_3 product with the concomitant formation of a degradation product whose nmr spectrum displays an unresolved absorption band at δ1.25-1.60. The mass spectrum of **2** displayed a strong parent ion at *m/e* 446.376 (calcd. for $C_{29}H_{50}O_3$ 446.375) with major fragmentations at *m/e* 415($M-OCH_3$), 414($M-HOCH_3$), 305($M-C_{17}$ side chain), and

219(M-A ring). The nmr spectrum ($COCl_3$) of 2 shows two distinct singlets for the nonequivalent methoxyls at δ 3.33 and 3.35, an AB quartet centered at δ 5.10 for the protons on the C-19 carbon, and two slightly broadened singlets at δ 5.87 and 6.02 for the vinyl protons.

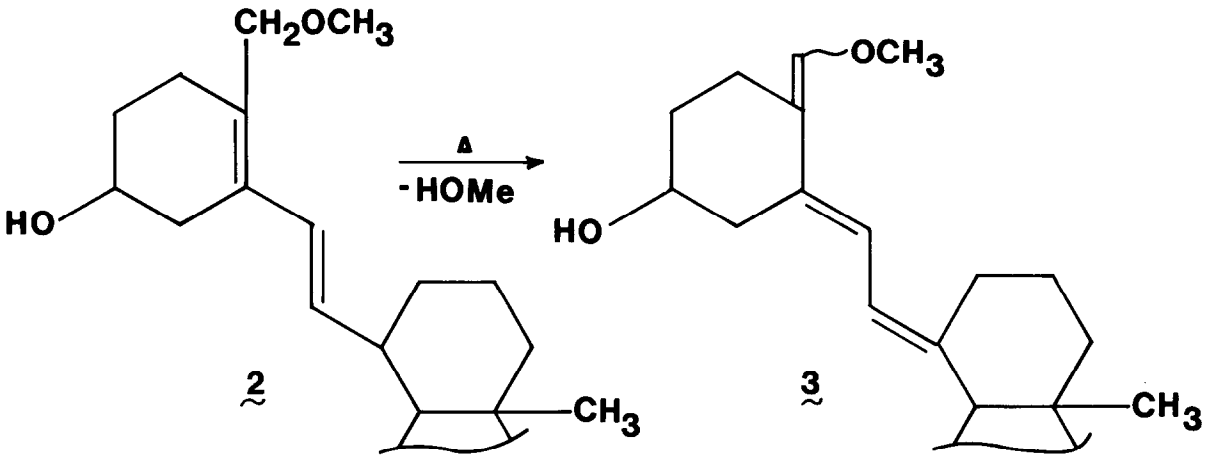
Allowing 2 to sit at room temperature for several hours led to 3 which was a mixture of Z and E isomers. The conversion of 2 to 3 could be followed by nmr with the formation of one equivalent of methanol. The mass spectrum of 3 displayed a strong parent ion at m/e 414.360 (calcd. for $C_{28}H_{46}O_2$ 414.358). The nmr spectrum ($CDCl_3$) of 3 displayed absorptions at δ 0.62 and 0.71 for the C_{18} methyl as well as two absorptions at δ 3.43 and 3.51 for the C_{19} methoxyl (Z and E isomers). The uv spectrum (aqueous ETOH) of 3 exhibits the bathochromic shift relative to 2 in going to the triene (2 λ_{max}=236nm; 3 λ_{max}=273nm).

A crystalline derivative[9] of 3 was obtained by treating 3 with aqueous acid to hydrolyze the enol ether. The mass spectrum of 4, mp 93-97°, displayed a strong parent ion at m/e 400.337 (calcd. for $C_{27}H_{44}O_2$ 400.334).

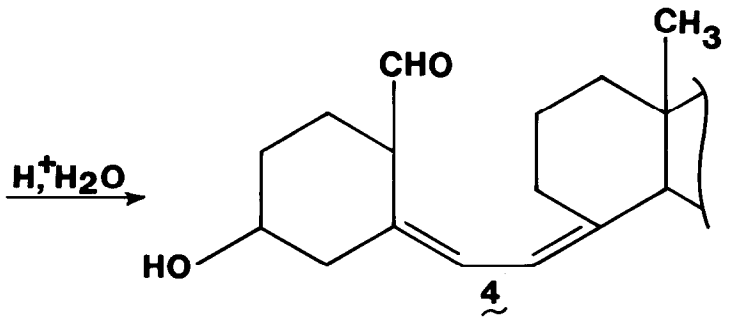
Our investigation shows that vitamin D_3 is readily susceptible to attack by singlet oxygen and leads to a novel product due most probably to the propensity of the intermediate dioxolane to suffer attack by solvent. Some enzymatic oxidations have been speculated to involve the intermediacy of singlet oxygen[10], and it appears possible that vitamin D_3 may be degraded by this reactive oxidant *in vivo*.


CH3
CH3
CH3
CH3
CH2
HO
O2 /0°
MeOH

1


CH2OCH3
HO
Δ
-HOMe
OCH3
HO
CH3
CH3

2 3


CH3
CHO
H,+H2O
HO

4

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