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SYNTHESIS OF 6,19-EPIDIOXY-9,10-SECOERGOSTA-5(10),7,22-TRIEN-3β-OLS FROM VITAMIN D DERIVATIVES BY OXIDATION WITH SINGLET OXYGEN

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Since exciting development in the study of the metabolism of vitamin D was achieved,[1] considerable attention has been directed towards the chemistry of vitamin D.[2] Vitamin D derivatives have been known to be sensitive for air oxidation or oxidation by singlet oxygen probably due to the presence of *s-cis* diene function in the molecule. Singlet oxygen has also been known to be a powerful biological oxidant and a number of reports describing oxidation of biological substances by singlet oxygen has been published.[3] However, oxidation of vitamin D by singlet oxygen has not been extensively studied, except for the recent report by Bland et al.[4] who studied oxidation of vitamin D_3 by chemically generated singlet oxygen (sodium hypochlorite-hydrogen peroxide) Instead of isolating the expected epidioxide (**2c** and/or **3c**), they isolated 8,19-dimethoxy-9,10-secocholesta-5(10),6-dien-3β-ol (**4**) and suggested that the latter product was formed from the primary produced epidioxide (**2c** and/or **3c**) by the reaction with methanol used as the solvent in the reaction.

In this paper, we would like to report the first synthesis of 6,19-epidioxide of vitamin D_2 derivatives (**2** and **3**) by a dye sensitized photo-oxidation.

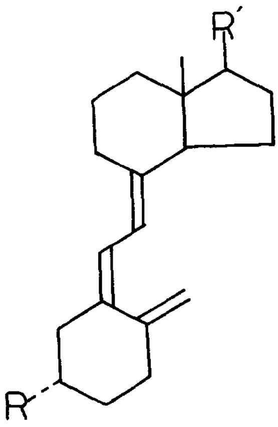
A solution of vitamin D_2 benzoate (**1a**) (1 g) in 95% ethanol containing pyridine (0.5% v/v) and Rose Bengal (1/5 equiv) was irradiated under current of oxygen with halogen lamp (200 W) until all of the starting vitamin was consumed (7 hr). After evaporation of the solvent, the residue was filtered through a short column of alumina and chromatographed on silica gel to afford two isomeric peroxides 2a: mp 132-133° and 3a: mp 126-127° in the yields of 18% and 25%, respectively. The structure of 2a and 3a was determined to be C-6 epimers of 6,19-epidioxy-9,10-secoergosta-5(10),7,22-trien-3β-ol benzoate from their spectral properties and satisfactory elemental analysis ($C_{35}H_{48}O_4$). The mass spectra of 2a and 3a were quite similar and each exhibited very weak molecular ion at m/e 532 and fragmentation ions at m/e 514 ($M^+ - H_2O$) and 392 ($M^+ - H_2O - C_6H_5COOH$). The UV spectra of 2a and 3a [$\lambda_{max}^{95\%\ EtOH}$ nm (log ε) 2a: 207 (4.35), 227 (4.19), 273 (3.02), 281 (2.98); 3a: 209 (4.30), 229 (4.18), 274 (3.09), 281 (3.04)] were quite similar each other and did not show maximum absorption at 265 nm indicating the absence of the conjugated triene system. The ^1H NMR spectra (100 MHz) of 2a and 3a were also quite similar [δ ($CDCl_3$) J in Hz 2a: 0.59 (3H, s), 0.82 (3H, d, J = 7), 0.84 (3H, d, J = 7), 0.92 (3H, d, J = 7), 1.02 (3H, d, J = 7), 4.3 (1H, d, J = 15), 4.56 (1H, d, J = 15), 4.88 (1H, d, J = 10), 5.18 (2H, m), 5.32 (1H, d, J = 10), 5.4 (1H, m), 7.3-7.6 (3H, m), 8.01 (2H, dd, J = 8 and 2); 3a: 0.59 (3H, s), 0.83 (3H, d, J = 7), 0.84 (3H, d, J = 7), 0.92 (3H, d, J = 7), 1.03 (3H, d, J = 7), 4.21 (1H, d, J = 16), 4.63 (1H, d, J = 16), 4.78 (1H, d, J = 10), 5.18 (2H, m), 5.30 (1H, d, J = 10), 5.25 (1H, m), 7.3-7.6 (3H, m), 8.01 (2H, dd, J = 8 and 2)] and showed an AB quartet for the C-19 protons, a doublet for C-6 proton, and a broad doublet for the C-7 proton. The ^{13}C NMR spectra of 2a and 3a afforded further supporting evidence for the assigned structure exhibiting 32 and 33 signals respectively, eleven of them being the signals due to SP^2 carbon atoms [δ ($CDCl_3$) 2a: 115.0, 125.4, 125.9, 128.3, 129.5, 130.5, 132.0, 132.8, 135.4, 149.0, 165.9; 3a: 114.3, 125.9, 126.4, 128.2, 129.5, 130.4, 132.0, 132.8, 135.4, 149.6, 165.9], and three of them being the signals due to the SP^3 carbon atoms bonded to oxygen (2a: 69.0, 72.2, 76.7; 3a: 70.6, 72.1, 76.8).

Similar photo-oxidation of vitamin D_2 (1b) gave a mixture of two epimeric epidioxides (2b and 3b) as colorless crystals (35%), mp 101-102°, *m/e* 428 (M^+), 410 ($M^+ - H_2O$), 285 ($M^+ - H_2O$ - side chain), UV $\lambda_{max}^{95\%\ EtOH}$ 210 nm (log ε = 4.21), NMR δ($CDCl_3$) J in Hz 0.58 (3H, s), 0.82 (3H, d, J = 7), 0.84 (3H, d, J = 7), 0.92 (3H, d, J = 7), 1.01 (3H, d, J = 7), 3.95-5.40 (7H, m), which could not be resolved either by TLC (silica gel, ethyl acetate-hexane) or by HPLC (

μ-porasil Water's associate, i-propanol-hexane). By treatment with benzoyl chloride in pyridine followed by chromatographic separation (silica gel), this mixture gave two monobenzoates in about equal amount which were shown to be identical with 2a and 3a by mixed melting point determinations as well as by comparison of the spectral data. This fact showed clearly that only one hydroxy group was present in the starting epidioxides and, thus, provided a chemical evidence for the assigned structures.

The determination of the configuration at C-6 in 2a and 3a is progressing by X-ray crystallographic analysis and analysis of their CD spectra.[5]

The epidioxides (2 and 3) or compounds derived thermally from them are expected to be produced in vivo and it will be interesting to compare them with vitamin D metabolites unidentified so far.[6] On this point of view, studies on the chemical reactivities of the epidioxides prepared in the present work are now under progress.



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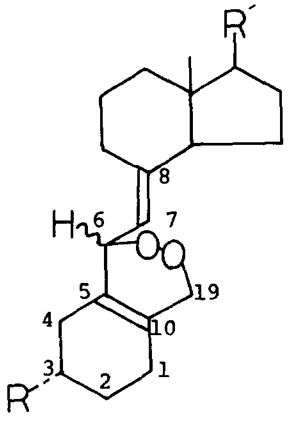
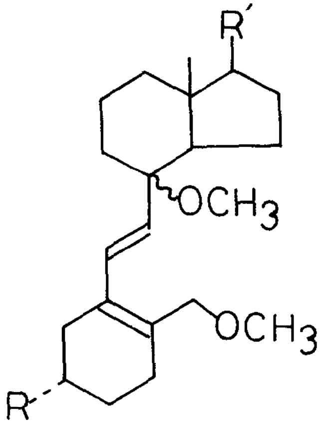


2 and 3



4

	a	b	c
R	$OCOC_6H_5$	OH	OH
R'	C_9H_{17}	C_9H_{17}	C_8H_{17}

References and Notes

(1) For recent review see H. F. DeLuca and H. K. Schnoes, *Ann. Rev. Biochem.*, **45**, 631 (1976).

(2) See, for example, R. M. Wing, W. H. Okamura, A. Rego, M. R. Pirio, and A. W. Norman, *J. Am. Chem. Soc.*, **97**, 4980 (1975). M. Sheves and Y. Mazur, *J. Am. Chem. Soc.*, **97**, 6249 (1975). D. J. Aberhart and A. C-T. Hsu, *J. Org. Chem.*, **41**, 2098 (1976).

(3) See, for example, C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968). N. I. Krinsky, Science, 186, 363 (1974). G. W. Grams, K. Eskins, and G. E. Inglett, *J. Am. Chem. Soc.*, **94**, 866 (1972).

(4) J. Bland and B. Craney, *Tetrahedron Lett.*, 4041 (1974).

(5) The CD spectra of **2a** and **3a** [$\Delta\varepsilon$(nm) **2a**: -14.9 (211), +9.2 (229); **3a**: +12.1 (210), +7.8 (221)] showed remarkably contrasting Cotton effect in the region of π-π^* transition of isolated double bond. Though there are three isolated double bonds in **2a** and **3a**, only the environment around 5(10)-double bond showed significant difference between **2a** and **3a**. This fact suggests that the latter double bond is responsible for the contrasting Cotton effect at around 210 nm. Based on this assumption, the configuration at C-6 was predicted to be S for **2a** and R for **3a** by the double bond Octant rule analysis. The confirmation of the assignment by X-ray crystallographic analysis is under progress.

(6) H. F. Holick, H. K. Schnoes, H. F. DeLuca, T. Suda and R. J. Cousins, *Biochemistry*, **10**, 2799 (1971). T. Suda, H. F. DeLuca, H. K. Schnoes, Y. Tanaka, and H. F. Holick, *Biochemistry*, **9**, 4776 (1970). G. Jones, H. K. Schnoes, and H. F. DeLuca, *Biochemistry*, **14**, 1250 (1975).

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