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Structure of the Endoperoxides derived from Vitamin D Derivatives by Dye Sensitized Photo-oxidation: X-Ray Crystal Structure of 6,19-Epidioxy-9,10-seco-5(10),7,22-ergostatrien-3β-ol Benzoate

The precise structures of the biologically potent endoperoxides derived from vitamin D_2, vitamin D_3, and their benzoates by dye sensitized photo-oxidation were established by X-ray analysis as well as by analysis of their circular dichroism spectra.

Keywords——endoperoxides; dye sensitized photo-oxidation; CD spectra; X-ray analysis; 1,4-cycloaddition reaction of singlet oxygen; biologically potent vitamin D analogue

In connection with the metabolism[1] and biological oxidation of vitamin D, we have been interested in the reaction of vitamin D with singlet oxygen and recently[2] reported the successful isolation of two crystalline peroxides (**1a** and **2a**) from vitamin D_2 benzoate by dye sensitized photo-oxidation. Although the structures of the peroxides were determined to be C-6 epimers of 6,19-epidioxy-9,10-seco-5(10),7,22-ergostatrien-3β-ol benzoate based on their spectral data, the configuration at C-6 has remained unsolved. In order to establish the structure including the configuration at C-6 of these biologically potent endoperoxides precisely,[3] we conducted an X-ray analysis of one of the epimers (**1a**).

Suitable crystals of the less polar peroxide (**1a**) for a single-crystal X-ray analysis were obtained by crystallization from acetone. The crystals were monoclinic $P2_1$ with cell dimensions of $a=16.753$, $b=7.446$, $c=13.572$ Å, and $\beta=111.4°$. Intensities were measured on a Philips PW1100 four-circle diffractometer using Cu-$K\alpha$ radiation monochromated by a graphite plate, and 3144 independent data were used for the analysis. The structure was elucidated by the direct method with program MULTAN.[4] Positional and thermal parameters were refined by the least-squares method to an R value of 0.092. The computer generated per-

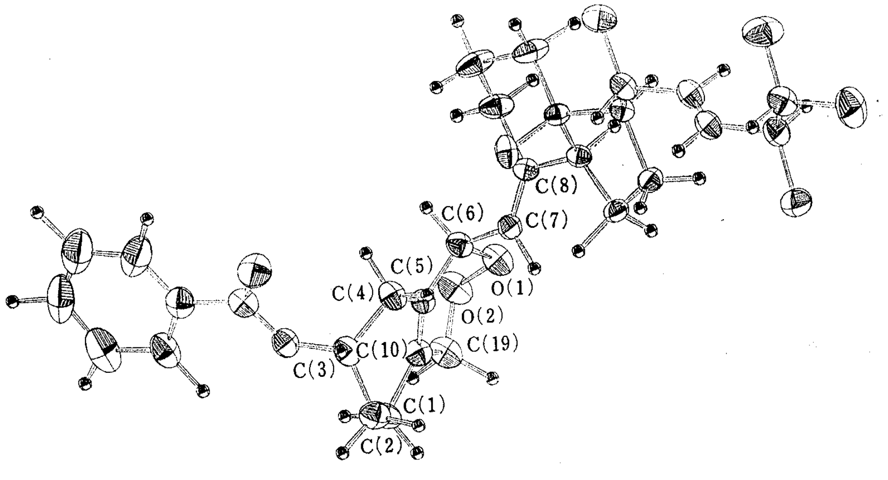

Fig. 1. Perspective View of **1a** (Co-ordinates of hydrogens of methyl groups could not be determined by the present X-ray analysis and are not shown.)

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[1] H.F. DeLuca and H.K. Schnoes, *Ann. Rev. Biochem.*, **45**, 631 (1976).

[2] S. Yamada, K. Nakayama, and H. Takayama, *Tetrahedron Lett.*, **1978**, 4895.

[3] These endoperoxides were found to have considerable biological activity in stimulating calcium transport as well as in bone mineral mobilization; S. Moriuchi, S. Yamada, K. Nakayama, and H. Takayama, to be published.

[4] G. Germain, P. Main, and M.M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).

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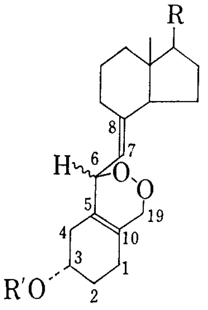
spective view of the molecule is shown in the Figure. As can be seen in the Figure, the configuration at C-6 in **1a** is *R*.[5] Since it has been shown that **2a** is the C-6 epimer of **1a**, the configuration at C-6 in **2a** was now determined to be *S*.

For the determination of the configuration at C-6 in the analogous endoperoxides derived from other vitamin D derivatives, comparison of circular dichroism (CD) spectra was found to be useful. In the CD spectra (Table) of the endoperoxides (**1a**, **b** and **2a**, **b**)[6] whose structures have been determined unequivocally, the Cotton effect observed at around 210 nm, the region of π-π^* transition of isolated double bond, was negative for the 6-*R* isomers (**1a** and **1b**) and positive for the 6-*S* isomers (**2a** and **2b**). Similarly contrasting Cotton effect was observed in the CD spectra of C-6 epimers of the endoperoxides (**1c**/**2c** and **1d**/**2d**) derived from vitamin D_3 derivatives (Table). This fact indicates that the configuration at C-6 has great effect on the determination of the sign of the Cotton effect and that the configuration could be deduced by comparison of their CD spectra. Accordingly, we assigned the endoperoxides which showed negative Cotton effect at around 210 nm as 6-*R* isomers and those which showed positive one as 6-*S* isomers. The assignments were further supported by comparison of their nuclear magnetic resonance spectral deta.[7]

Table I. CD Spectra in *n*-Hexane

Compound	λ/nm ($\Delta\varepsilon_{\max}$)
1a	211(−11.5), 227(+5.7)
1b	210(−17.7)
1c	209(−20.5), 228(+6.5)
1d	207(−23.2)
2a	206(+7.7), 219(+5.8)
2b	211(+11.3)
2c	210(+6.3), 221(+8.2)
2d	215(+6.5)



1: (6*R*)
2: (6*S*)

	R	R′
a	C_9H_{17}	C_6H_5CO
b	C_9H_{17}	H
c	C_8H_{17}	C_6H_5CO
d	C_8H_{17}	H

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[5] The configuration at C-6 could not be predicted correctly by analysis of their CD spectral data alone, see the note in the reference 2.

[6] The endoperoxides (**1b** and **2b**) were converted to the corresponding benzoates (**1a** and **2a**, respectively) and identified.

[7] The difference of the chemical shifts of the two C-19 protons is larger for the 6-*S* isomers and smaller for the 6-*R* isomers.

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