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STUDIES ON THE ADDUCTS OF SULFUR DIOXIDE WITH VITAMIN D

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Vitamin D_2 reacted rapidly with liquid sulfur dioxide at the $\Delta^{5,10(19)}$-diene part to give the α- and the β-face adducts in about 1:1 ratio. Both adducts extruded sulfur dioxide by thermolysis to give 5,6-trans vitamin D_2 in good yield together with a trace of vitamin D_2. Similar reactions were examined for vitamin D_3 and trans vitamin D_2.

Since active metabolites of vitamin D were found,[1] considerable attention has been directed toward the chemistry of vitamin D.[2] The s-cis diene part of the triene chromophore of vitamin D derivatives was reported to react readily with dienophile and the reactions with maleic anhydride[3] and 4-phenyl-1,2,4-triazoline-3,5-dione[4] have been reported. The s-cis diene part also reacts with diiron nonacarbonyl to form stable tricarbonyl iron complexes.[5] Whereas the Diels-Alder adducts do not revert to the starting vitamin by retro-Diels-Alder reaction, tricarbonyl iron group can be removed easily to reproduce the starting vitamin by simple oxidation with ferric chloride. By this reason tricarbonyl iron group has been used as a protecting group of the labile triene part of vitamin D.[5] Previously, we reported the reaction of vitamin D with singlet oxygen as a dienophile, successful isolation of oxygen adducts at the $\Delta^{5,10(19)}$-diene part,[6] and determination of the structure including the configuration at C-6 based on the X-ray analysis.[7] The endoperoxides derived from vitamin D_3 have been found to have considerable biological activities.[8]

Sulfur dioxide is also a powerful dienophile and the reversible addition reaction with conjugated double bond systems has been known as a typical cheletropic reaction.[9]

As part of continuing studies on the chemistry of vitamin D, we have investigated the reaction of vitamin D derivatives with sulfur dioxide as a possible protecting group of the s-*cis* diene part and found that vitamin D actually reacted spontaneously and quantitatively with liquid sulfur dioxide to give the adducts (2 and 3).

In a typical experiment, vitamin D_2 (400 mg) was dissolved in liquid sulfur dioxide at -20° and then the sulfur dioxide was evaporated to give a mixture of isomeric adducts (2a and 3a) in 55:45 ratio (determined by HPLC on ODS column using 15:85 water-methanol as solvent) in quantitative yield. Separation of the adducts was performed by chromatography on silica gel [Lobar column (Merck)] with 1:1 hexane-ethyl acetate giving the less polar adduct (2a) (239 mg) as a colorless glass and the more polar adduct (3a) (188 mg) as colorless crystals, mp 103° (decomp.). Both adducts showed quite similar spectroscopic and chemical properties. The UV spectra (95% EtOH) of 2a and 3a exhibited no absorption maximum above 220 nm indicating the absence of the triene chromophore. The IR spectra (KBr) of 2a and 3a showed absorption of SO_2 group at around 1300 and 1140 cm^{-1}. In the mass spectra, 2a and 3a showed no molecular ion peak even by chemical ionization method (methane was used as an ionizing gas) and two peaks were observed at m/e 397 $[(M^+ + 1) - SO_2]$ and 379 $[(M^+ + 1) - SO_2 - H_2O]$ for both adducts. In the ^1H NMR spectra (C_6D_6) of 2a and 3a, the signals of C-6 and C-7 protons appeared as a pair of doublets at δ 4.48 and 4.90 (J = 9 Hz) for 2a and δ 4.55 and 4.95 (J = 9 Hz) for 3a, C-3 proton at δ 3.75 as multiplet for both adducts, and the 18-methyl protons as a singlet at δ 0.75 for 2a and 0.48 for 3a. These spectral data are in good accordance with the assigned structure. The configuration at C-6 in the adducts was determined as follows. The CD spectra (95% EtOH) of 2a and 3a showed remarkably contrasting Cotton effect due to the isolated double bonds at 203 nm ($\Delta\varepsilon$ = +11.5) and 208 nm ($\Delta\varepsilon$ = -26.2), respectively. The CD spectra of the two C-6 epimers of the oxygen adducts of vitamin D_2 (4a and 5a) whose structures were determined unequivocally based on the X-ray analysis showed similarly contrasting Cotton effect at 211 nm ($\Delta\varepsilon$ = +11.3) for 4a [(6*S*)-isomer] and 210 nm ($\Delta\varepsilon$ = -17.7) for 5a [(6*R*)-isomer].[7] Comparison of the CD spectra of these structurally closely related pairs of compounds suggested the configuration at C-6 in the sulfur dioxide adducts to be *S* for 2a and *R* for 3a.

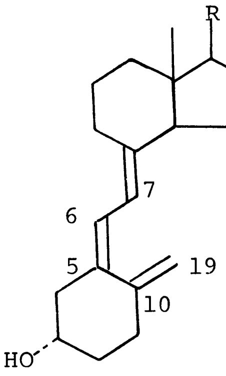
Both adducts (2a and 3a) extruded sulfur dioxide by thermolysis to give 5,6-*trans* vitamin D_2 (6a)[10] as a major product together with a trace of vitamin D_2 (1a).

Thus, by refluxing in ethanol, the adducts (2a and 3a) were completely decomposed within 2 h to give 6a in about 80% isolated yield. These results are in good accordance with the precedents[9] of thermal decomposition of sulfur dioxide adducts in which trans isomers were produced exclusively when the production of both cis- and trans-isomers were allowed by the symmetry rule.[11]

Trans-vitamin D_2 (6a) similarly reacted with liquid sulfur dioxide to give the same adducts obtained from vitamin D_2 (2a and 3a) in the 1:1 ratio quantitatively. Vitamin D_3 (1b) also gave the adducts (2b and 3b) in the 1:1 ratio by the same reaction. The adducts (2b and 3b), however, afforded the starting vitamin (1b) and trans vitamin D_3 (6b) in the 1:1 ratio by the similar thermolysis.

Further studies on the chemical reactivity of the adducts (2 and 3) are in progress.

The biological activity of the adducts (2 and 3) is also interesting compared with that of the oxygen adducts (4 and 5) and is also being tested.



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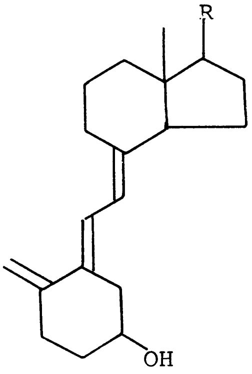

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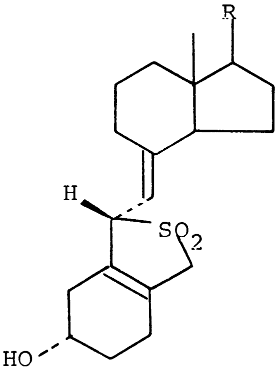

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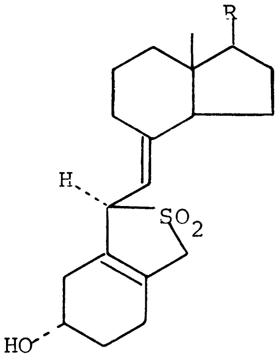

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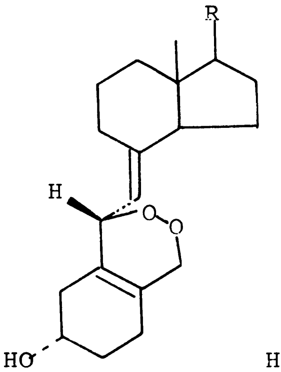

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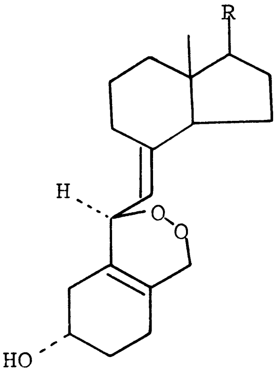

5

	R
a	C_9H_{17}
b	C_8H_{17}

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