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A Convenient Synthesis of Vitamin D_3-9, 19-^3H and the Mechanism of the Previtamin $D_3 \rightleftharpoons$ Vitamin D_3 reaction

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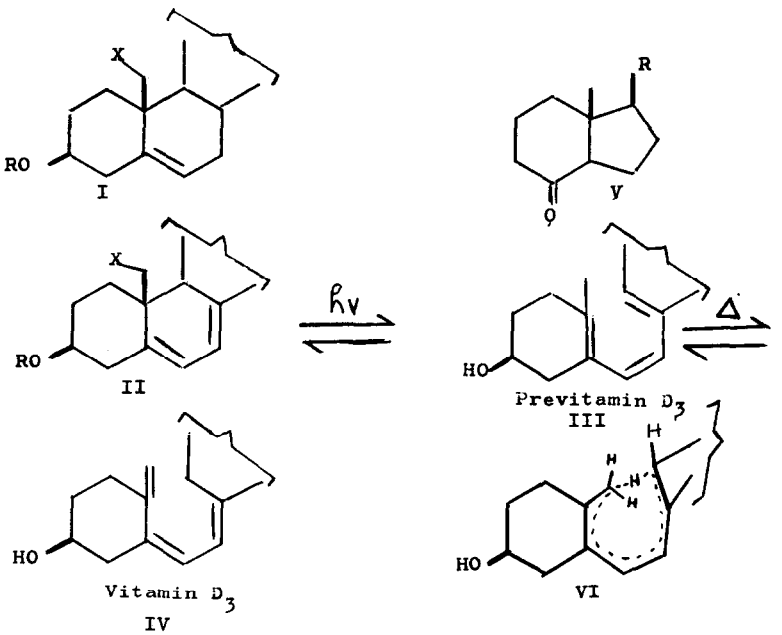
A recent communication[1] prompts us to report our results on the previtamin $D_3 \rightleftharpoons$ Vitamin D_3 reaction. The crucial intermediate, 19-tritiated cholesterol, required for our mechanistic work was synthesised as follows. 19-tosyl cholesteryl acetate[2] (I, R = Ac, X=$OSO_2C_6H_4CH_3$ p) with sodium iodide in boiling ethyl methyl ketone gave the 19-iodide (I, R = Ac, X = Iodine) which on reduction with zinc in the presence of tritiated water, containing a trace of acid, gave cholesteryl acetate-19-^3H(I, R = Ac, X =^3H).[3] The latter gave 7-dehydrocholesterol-19-^3H(II, R = H, X = ^3H) which on photolysis yielded previtamin D_3-19-^3H (III) and this on thermal rearrangement gave tritiated vitamin D_3 (IV) isolated as its 3,5-dinitrobenzoate. Radioactivity measurements revealed that no significant amount of label was lost during

the conversions II (R = H; activity 1.08)⟶IV (activity 1.00) and III (activity 1.05)⟶IV (activity 1.00). Furthermore, a sample of tritiated vitamin D_3 3,5-dinitrobenzoate after being refluxed for two hours in methanol-benzene showed no loss of radioactivity.

These results conclusively establish the previously postulated mechanism[4] in which the conversion III $\rightleftharpoons$ IV takes place through an intramolecular hydrogen transfer. We hoped that distribution of radioactivity between C-19 and C-9 in vitamin D_3 (IV) would throw some light on the stereochemistry of the transition state (VI) involved in the reversible reaction III $\rightleftharpoons$ IV. A stereospecific delivery and migration of hydrogen atom in the transition state VI for the conversion III $\rightleftharpoons$ IV would be indicated by a 2:1 distribution of radioactivity between C-19 and C-9 while a 1:1 distribution between positions 9 and 19 would indicate a non-stereospecific transition state in which both 9α and 9β hydrogen atoms are equivalent. On ozonolysis vitamin D_3-9,19-^{3}H (IV) gave formaldehyde which was isolated as its dimedone derivative and which had 48% of the radioactivity of vitamin D_3. The latter on oxidation with acidic potassium permanganate gave the ketone (V) which was isolated as its semicarbazone derivative and which had only 3% of the radioactivity of vitamin D_3, most of the label having been lost during oxidation. From these experiments we conclude that thermal equilibration of III and

IV takes place through intramolecular hydrogen transfer and the transition state leading to this process is non-stereospecific. This is illustrated in Fig. VI although for the sake of convenience we have shown the transition state as involving only the α-hydrogen.



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