Equilibria in Vitamin D_3. Preparation and Properties of 6-Methylvitamin D_3 and its Isomers

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Summary 6-Methylvitamin D_3 and its isomers, the corresponding previtamin, *trans*-vitamin, and tachysterol were prepared from 6-oxo-3,5-cyclovitamin D_3; their relative thermodynamic stabilities were established, and compared with the stabilities of the respective vitamin D_3 isomers.

THE biosynthesis of vitamin D involves thermal equilibrium between previtamin D and vitamin D.[1] The 1,7-H sigmatropic shift which occurs in these reactions is unable to take place from the *s-trans* conformation of these compounds [as shown in (**2a**) and (**4a**)] predominant at room temperature.[1] Rotation around the 5,6- and 6,7-bond in (**2a**) and (**4a**) is necessary to achieve the *s-cis* conformation required for the sigmatropic shift of the hydrogen. To investigate the influence of steric interactions on these rotations and thus on the previtamin D–vitamin D equilibrium, we have synthesized 6-methylvitamin D_3 (**2b**) and have studied its physical properties and isomerizations.

TABLE 1. Thermal and I_2-induced equilibrium ratios.

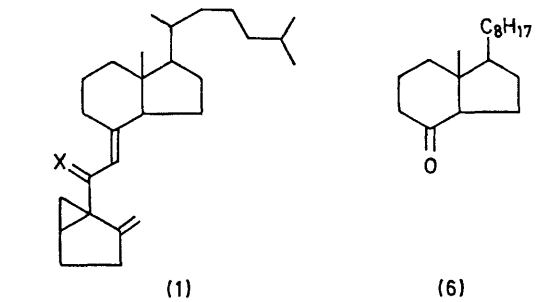
Equilibrium	6-H series	6-Me series
5,6(*Z*) ⇌ 6,7(*Z*)	(**2a**) : (**4a**) 80 : 20	(**2b**) : (**4b**) >99% (**4b**)
5,6(*Z*) ⇌ 5,6(*E*)	(**3a**) : (**2a**) 70 : 30	(**3b**) : **2b**) 85 : 15
6,7(*Z*) ⇌ 6,7(*E*)	(**5a**) : (**4a**) >99%(**5a**)	(**5b**) : (**4b**) 50 : 50

[a] Data from ref. 1.

Since the traditional photochemical route for the preparation of vitamin D_3 (**2a**)[1,2] and its analogues failed, we used a new approach, utilizing the 3,5-cyclovitamin D_3 recently described by us,[3] as intermediates. The 6-oxo-3,5-cyclovitamin D_3 (**1a**),[4] obtained in three steps from vitamin D_3

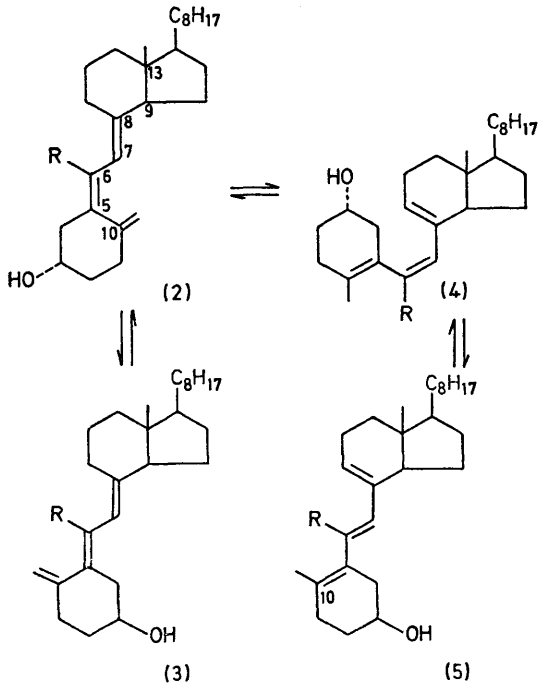
(**2a**), was converted with methyl-lithium into a 3 : 1 mixture of the two isomeric 6-methyl alcohols (**1b**)† (90%). Solvolysis of either isomer of (**1b**) in aq. dioxan in the presence of toluene-*p*-sulphonic acid resulted in a 1 : 1 mixture of 6-methylvitamin D_3 (**2b**) and 6-methyl-*trans*-vitamin D_3 (**3b**).

The presence of the 7,8 double bond in both (*Z*) and (*E*) isomers about the 5,6 double bond, (**2b**) and (**3b**), indicated by a comparatively high-field chemical shift of their 13-Me protons (δ 0·55),‡ was established by the formation of the analogue of Grundman's ketone upon their ozonolysis. The respective (*Z*)- and (*E*)-configurations of the 5,6-double bonds in (**2b**) and (**3b**) were deduced from their thermal behaviour. The former isomer undergoes a thermal 1,7-H shift to give 6-methyl-previtamin D_3 (**4b**) while the latter is thermally stable. The equilibrium (**2b**) ⇌ (**4b**) was found to lie completely in favour of (**4b**) since it is recovered unchanged after 12 h at 90 °C, while short heating of (**2b**) at the same temperature results in complete isomerization (Table 1).



(1) (6)

a, X = O
b, X = Me,OH



(2) (4) (3) (5)

a; R = H
b; R = Me

Compounds (**2b**) and (**4b**) undergo isomerization with visible light in the presence of I_2 to give the *trans* compound (**3b**) and 6-methyltachysterol (**5b**) respectively. Both isomerizations were found to be reversible, the (*Z*) : (*E*) equilibrium ratios being 85 : 15 and 50 : 50 for (**3b**) : (**2b**) and (**5b**) : (**4b**) respectively (Table 1).

The u.v. spectra of the 6-methyl isomers differ considerably from those of analogues with the 6 position unsubstituted, their absorption maxima being shifted to the shorter wavelength and their ε values being lower (Table 2). These changes in the u.v. spectra are attributed to the deviation from planarity in both ground and excited states. Thus in (**2b**) and (**3b**) the 6,7 bond is twisted to alleviate the 6-Me–9-H steric hindrance. The introduction of a 6-methyl group into tachysterol (**5a**) increases considerably the average torsional angles around the 5,6 as well as the 7,8 bonds owing to the respective 6-Me–10-Me and 6-Me–9-H interactions. In (**4a**) the ring A and ring C/D planes are presumably already tilted in relation to each other;[1] therefore, the 6-Me–10-Me interaction in the 6-methyl analogue (**4b**) increases this distortion only slightly, explaining the relatively small values of the blue shift (Table 2).

TABLE 2. U.v. spectra in Et_2O, room temperature, λ_{max}/nm values ($\epsilon \times 10^{-4}$).

Isomers	6-H series[a]	6-Me series	Δ[b]
5,6(*Z*)	(**2a**) 264(1·7)	(**2b**) 239(0·9)	25
5,6(*E*)	(**3a**) 272(2·3)	(**3b**) 242(1·1)	30
6,7(*Z*)	(**4a**) 261(1·0)	(**4b**) 247(1·0)	14
6,7(*E*)	(**5a**) 285(2·5)	(**5b**) 238(1·0)	47

[a] Data from refs. 1 and 2; [b] λ_{max} differences between the 6-H and 6-Me series.

The changes in the u.v. spectra reflect the relative stabilities in the two series of compounds (Table 1). Thus these steric interactions of the 6-methyl group are responsible for the relatively high thermodynamic stability of (**4b**) which predominates in the (**2b**) ⇌ (**4b**) equilibrium and the equal proportions of (**4b**) and (**5b**) in the (**5b**) ⇌ (**4b**) equilibrium.

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† Analytical data, full analysis of ^1H and ^{13}C n.m.r. spectra, and mass spectra of all the new compounds will be published in a full paper.

‡ The chemical shifts for 13-Me are indicative of the position of the double bonds at ring C; the resonances are at δ *ca.* 0·55, 0·70, and 0·90 for Δ^7, $\Delta^{8(9)}$, and $\Delta^{8(14)}$ compounds, respectively.

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