Conformation Equilibria in Vitamins D. The Synthesis of 1α-Hydroxy-3-epivitamin D_3 (1α-Hydroxy-3α-cholecalciferol)

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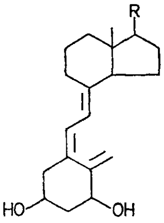
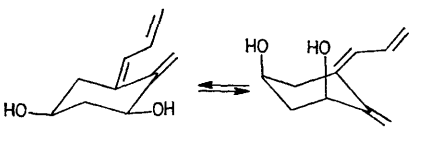
Summary The ratio of the two conformers of 1α-hydroxy-3-epivitamin D_3, which has been synthesized from 1α,3β-dihydroxycholest-Δ^6-ene, has been established.

Recent ^{1}H n.m.r. studies of cholecalciferol[1] and ergocalciferol[2] (vitamin D_3 and D_2) have confirmed Havinga's suggestion of a rapid equilibrium in solution between two, almost equally populated, ring A α and β-chair conformations (in which the $=CH_2$ group lies below and above the ring plane respectively).[3] A similar conformational equilibrium was also found for the related 1,3-*trans*-diol, the biologically potent 1α-hydroxycholecalciferol[1] and it was proposed that its hormonal activity was related to the fact that the β-conformation has an equatorial OH substitutent at C(1).[1,4] We have now synthesized the 3-epimer of 1α-hydroxycholecalciferol, the 1,3-*cis*-diol, in order to find the ratio of the two conformers, and to establish its biological activity.

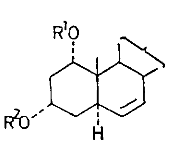
The starting material was the previously described 1α,3β-dihydroxycholest-Δ^6-ene[5] which was epimerized at C(3) ($EtCO_2N{=}NCO_2Et{-}Ph_3P$-*p*-nitrobenzoic acid in THF[6]) resulting in the 1α,3α-diol 3-*p*-nitrobenzoate (**2a**) m.p. 183—184°. Hydrolysis (5% KOH in MeOH) to the diol (**2b**) (75% from the starting diol) (m.p. 207—208°) followed by acetylation (*N*-dimethylaminopyridine–Ac_2O in CH_2Cl_2) led to the diaxial diacetate (**2c**) [m.p. 95—96°, δ ($CDCl_3$) 4·85 (1H, t, 1β-H, *J* 3 Hz, and δ 5·16 (1H, quintet, 3β-H, *J* 3 Hz)], which on bromination (Br_2 in CH_2Cl_2) gave the dibromide (**3**) (69% from (**2a**)] (m.p. 120—121°). The dibromide (**3**) was dehydrobrominated ($HMPA{-}Et_3MeN^+{-}Me_3PO_2^-{-}CaCO_3$, 110°, 10 h)[6,7] to a 5 : 1 mixture of the $\Delta^{4,6}$-diene (λ_{max} 236, 240, and 249 nm) and the $\Delta^{5,7}$-diene (λ_{max} 281, 292 nm). The $\Delta^{5,7}$-diene (**4**) was irradiated, without isolation, in Et_2O (Rayonet, 300 nm, $NaNO_3$ filter, 0°, 40 min) then heated at 70° for 2 h, and hydrolysed (5% KOH in MeOH, 0°, 0·5 h) resulting in a mixture from which (**1**), m.p. 114—116°, [λ_{max} 264 nm (ε 17·00) and on addition of I_2, λ_{max} 272 nm] was isolated [5% from (**3**)] by t.l.c. This compound shows identical peaks in the mass spectrum and a similar ^{1}H n.m.r. spectrum to its epimer 1α-hydroxycholecalciferol.[8] In the ^{1}H n.m.r. spectrum of (**1**) δ ($CDCl_3$), 5·00 (1H, d, 19*Z*-H, *J* 2), 5·28 (1H, m, 19*E*-H), 6·01



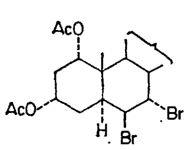
(1)



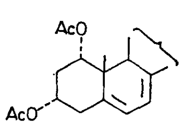
(1-β) (1-α)



(2a) $R^1=H, R^2=p\text{-}NO_2C_6H_4CO$
(2b) $R^1=R^2=H$
(2c) $R^1=R^2=Ac$



(3)



(4)

(1H, d, 6-H, *J* 11·5), and 6·40 (1H, d, 7-H, *J* 11·5 Hz) the protons at C(1) and C(3) appear at 4·04 and 4·30 p.p.m. as triplet and quintet respectively with an identical *J* 4·4 Hz. Assuming this coupling constant represents an averaged value of $^3J_{axax}$ 11 Hz and $^3J_{eqeq}$ 3 Hz, the calculated proportion of the two conformers (**1**-α) and (**1**-β) in $CDCl_3$ is 80:20.[9] It appears that the preponderance of the 1,3-diaxial conformer in solution derives from the H-bonding between the two OH groups.[10]

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