Convenient Synthesis of Crystalline 1α,25-Dihydroxyvitamin D_3

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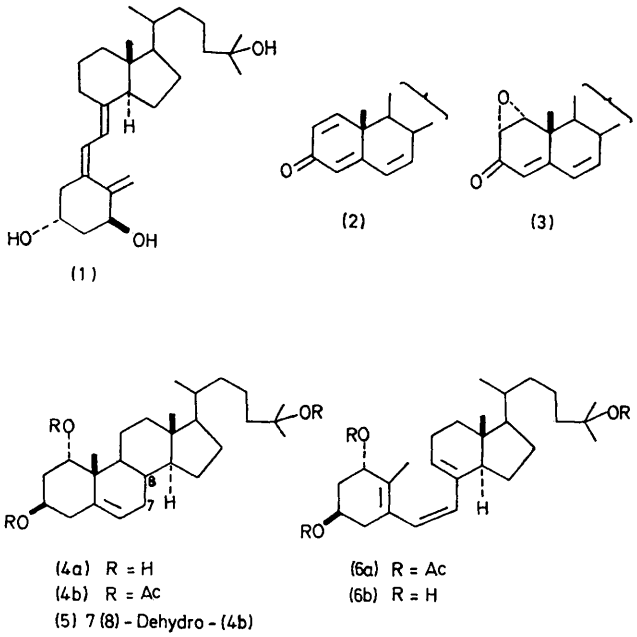
Summary Crystalline 1α,25-dihydroxyvitamin D_3 has been prepared from 25-hydroxycholesterol through an efficient eight-step synthesis.

ALTHOUGH the substance has never been obtained crystalline or adequately characterized by physical constants the structure (**1**) 1α,25-dihydroxyvitamin D_3, has been attributed to the important, rapid-acting, natural metabolite of vitamin D_3.[1] A 21-step synthesis of (**1**) has recently been claimed,[2] but again the compound was not obtained crystalline and its physical properties as well as those of key synthetic intermediates were not given.

We have recently reported a convenient synthesis of 1α-hydroxyvitamin D_3 involving as a key step the reductive conversion of a 1α,2α-epoxy-4,6-dien-3-one into a 1α,3β-dihydroxy-5-ene sterol.[3] We now report the application of this procedure to an efficient, unambiguous synthesis of crystalline 1α,25-dihydroxyvitamin D_3 and record here the physical properties thereof.†

Dehydrogenation (dichlorodicyanoquinone[3,4]) of 25-hydroxycholesterol[5] afford the trienone (**2**) (m.p. 183–184°, $[\alpha]_D$ −12°) which was converted (alkaline H_2O_2) into the epoxide (**3**) (m.p. 162—163°, $[\alpha]_D$ + 179°). Reduction of the epoxide (**3**) (metallic and NH_4Cl in ammonia-tetrahydrofuran[3]) led to the important intermediate 1α,25-dihydroxycholesterol (**4a**) {m.p. 171—173° (solidifies and remelts 178—179°), $[\alpha]_D$ −35°, ^1H n.m.r. 0·67 (3H, s, 13-Me), 1·02 (3H, s, 10-Me), 1·20 (6H, s, 25-Me_2), 3·86 (2H, narrow m, 1-H, and br m 3-H), 5·60 (1H, narrow m 6-H)}. Conversion of (**4a**) into the triacetate (**4b**) (Ac_2O–pyridine) followed by bromination (dibromodimethylhydantoin[6]) and dehydrobromination (trimethyl phosphite[6]) afforded the usual mixture of dienes from which the desired $\Delta^{5,7}$-diene triacetate (**5**)[2] was isolated by chromatography on $AgNO_3$-impregnated silica gel (m.p. 96—101°, $[\alpha]_D$ −24°). Irradiation of (**5**) (medium-pressure mercury lamp[3]) led to a mixture of photo-isomers from which the remaining diene (**5**) was recovered by chromatography on $AgNO_3$-impregnated silica gel. The balance of the irradiation product, which comprised largely the previtamin triacetate (**6a**) (based on the iodine-catalysed transformation of the previtamin into the tachysterol analogue[7]) was heated at 70° for 2 h to effect equilibration of (**6a**) and the triacetate of (**1**). Saponification (5% KOH in MeOH) led to a mixture of triols from which



† All new compounds had the appropriate spectral properties and, with the exception of the non-crystalline (**4b**) and (**6**), had the required composition (combustion microanalysis). All $[\alpha]_D$ are in $CHCl_3$ except for 1α,25-dihydroxyvitamin D_3. $\lambda_{max.}$ data are in nm and n.m.r. data in δ for $CDCl_3$ solution.

the desired (**1**) was isolated by preparative t.l.c. 1α,25-Dihydroxyvitamin D_3 (**1**) precipitated from ether with hexane had: m.p. 84—88°, $[\alpha]_D$ +29° (in Et_2O), λ_{max} (Et_2O) 264 (18,000), λ_{min} 228·5 (10,100), ^1H n.m.r. 0·57 (3H, s, 18-Me), 1·13 (6H, s, 25-Me_2), 4·85 and 5·30 (2H, double narrow m 10-CH_2), and 6·20 (2H, AB q, J 11·5 Hz, 6- and 7-H). Crystallized from $CHCl_3$ (**1**) was obtained as the mono-chloroform solvate, m.p. 106—112°. On treatment with I_2 (**1**) underwent a smooth transformation accompanied by spectral changes analogous to those accompanying the transformation of vitamin D_3[8] and 1α-hydroxyvitamin D_3[3] into the corresponding 5,6-*trans*-isomers. These physical and spectral properties are consistent with and required by structure (**1**) and are not compatible with any of the other triene isomers (or transformation products thereof) encountered in the vitamin D_3 series.

Preliminary biological data indicate that the 1α,25-dihydroxyvitamin D_3, (**1**) has the expected properties as evidenced by its ability to raise rapidly the level of serum calcium in parathyroidectomized–thyroidectomized rats. Our synthesis is a confirmation of the proposed structure.

Since the completion of this work additional syntheses of 1α-hydroxyvitamin D_3 have been reported.[9,10] Recently[11] a synthesis of 1α,25-dihydroxycholesterol (**4a**) has been described.

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