Synthesis of Active Forms of Vitamin D. Part IX.[1] Synthesis of 1α,24-Dihydroxycholecalciferol

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24-Oxocholesterol (1) (readily available from fucosterol) was converted by three steps into 1α,24ξ-dihydroxycholesterol (4). From the corresponding triacetate (5), 1α,24ξ-dihydroxycholecalciferol (9) was prepared *via* the 5,7-diene (8). The C-24 epimers of compound (4) were resolved by silica gel column chromatography of the monohydroxydibenzoates (7), and were separately transformed into the corresponding 1α,24-dihydroxycholecalciferol epimers.

VARIOUS metabolites of vitamin D_3 have been isolated recently, some of which may be the biologically active forms of the vitamin.[2] This has stimulated the synthesis of vitamin D analogues with hydroxy-groups at positions 25,[3-6] 24 and 25,[7,8] 25 and 26,[9] 1α and 25,[10,11] and 1α, 24, and 25.[1] In addition to these metabolic products, artificial ' analogues such as 1α-,[12-17] 4α-,[18] 22-,[19] and 24-hydroxy-[20] and 20,25-dihydroxy-[21] cholecalciferol, as well as the 1α-hydroxy-3-deoxy-derivative[22,23] have been synthetic targets. We have synthesized several key intermediates[24-28] for the preparation of these compounds from fucosterol, a marine sterol which is abundant in brown algae.[29] From one of these intermediates, the epimeric 24-hydroxycholecalciferols †,‡ were prepared, and were found to be active in stimulating intestinal calcium transport in rats deficient in vitamin D.[20] A significant difference of biological activities was noted between the 24-isomers.[33] That nephrectomy abolishes the intestinal calcium responses suggested that these compounds required a 1-hydroxy-group for biological activity.

We now report a synthesis of 1α,24ξ-dihydroxycholecalciferol. Both 24-epimers have also been prepared, in order to elucidate the effect of configuration on vitamin D activity.

24-Oxocholesterol (1), readily available from fucosterol,[27] was oxidized with 3.3 equiv. of dichlorodicyanobenzoquinone (DDQ)[34] in refluxing dioxan to afford, the 1,4,6-triene-3,24-dione (2) in 52% yield. The same trienedione (2) was also prepared from 24-oxocholestenone,[32] an ozonolysis product of fucostenone, by

† The configuration at C-24 of 24-hydroxycholesterol has been determined by Klyne and Stokes.[30] However, van Lier and Smith[31] suggested that this assignment should be reversed, and some uncertainty still remains. We will therefore retain the original nomenclature[32] for the present paper, referring to the epimers as 24ξ[1]- and 24ξ[2]-cholesterol (see Experimental section).

‡ *Note added in proof*: We have now determined the absolute configurations at C-24 of 24-hydroxycholesterol and related compounds. 24ξ′ and 24ξ[2] in this paper are 24*S* and 24*R*, respectively (N. Koizumi, M. Morisaki, N. Ikekawa, A. Suzuki, and T. Takeshita, *Tetrahedron Letters*, in the press).

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successive dehydrogenations with chloranil–t-butyl alcohol [35] and DDQ–dioxan.[36] Treatment of the trienedione (2) with alkaline hydrogen peroxide gave the 1α,2α-epoxide (3) (71%), which was reduced with lithium–ammonium chloride in liquid ammonia–tetrahydrofuran,[11,13] yielding 1α,24ξ-dihydroxycholesterol (4) (68% yield).

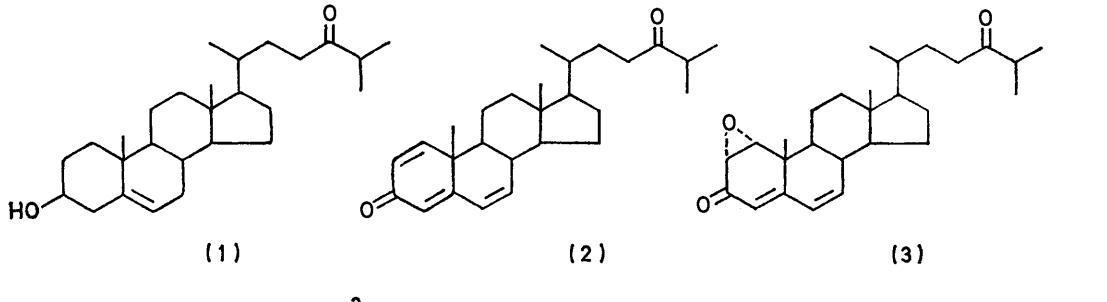
Compound (4) was converted either into the triacetate (5), for transformation into 1α,24ξ-dihydroxycholecalciferol (9), or into the 1α-hydroxy-3,24-dibenzoates (7) for the resolution of the 24-epimers. When the triol (4) was treated with 2.5 equiv. of benzoyl chloride in pyridine, the product showed three spots on t.l.c. (extended ascending irrigation method [37]). The least polar compound was identified as the tribenzoate (6) and others were found to be the epimeric dibenzoates (7) by n.m.r. analysis, after separation by silica gel column chromatography. The ^1H n.m.r. spectra of the isomers were almost identical, in contrast with those of 24,25-dihydroxy-derivatives, in which the 13-methyl signals of (24*R*)-compounds appeared at lower field ($\Delta\delta \simeq 0.06$ p.p.m.) than those of (24*S*)-isomers.[1]

The triacetate (5) was brominated with dibromodimethylhydantoin–hexane [38] and the resulting 7-bromo-compound was dehydrobrominated with *s*-collidine–xylene. U.v. analysis of the crude product indicated the presence of 5,7- and 4,6-dienes. The 5,7-diene (8) (37% yield) was isolated by saponification followed by t.l.c. on silver nitrate-impregnated silica gel.

Irradiation [39] of the 5,7-diene (8) in ether with a medium-pressure mercury lamp gave a mixture of photoisomers which was refluxed in benzene to effect thermal isomerization of precalciferol into calciferol. The desired vitamin D (9) was isolated (12% yield) by preparative t.l.c. on silver nitrate-impregnated silica gel.

For the preparation of the individual C-24 epimers, the separated dibenzoates (7) were converted into 1-acetates, which were then treated with *N*-bromosuccinimide–carbon tetrachloride. The products were dehydrobrominated with trimethyl phosphite–xylene [38] and the individual 5,7-dienes (8) were isolated by way of the cyclic adduct with 4-phenyl-1,2,4-triazoline-3,5-dione.[40]

By essentially the same method as described for the 24ξ-compound (8), the individual C-24 epimers were converted into the corresponding 1α,24-dihydroxycholecalciferols (9). The biological activity of the products and their absolute configuration at C-24 are under investigation.



EXPERIMENTAL

M.p.s. were determined with a hot-stage microscope apparatus. U.v. spectra were obtained with a Hitachi ESP-3T instrument for solutions in ethanol. N.m.r. spectra were determined with a Varian T-60 or a JEOL PS/PFT-100 spectrometer for solutions in deuteriochloroform unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra were run with a Shimadzu LKB-9000S spectrometer.

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Column chromatography was effected with silica gel (Wakogel C-200). T.l.c. was carried out on Merck silica gel F_{254} (0.25 mm thick). Silver nitrate-impregnated t.l.c. plates were prepared by dipping into 2% $AgNO_3$ solution in acetonitrile, followed by activation at 80 °C for 1 h.

Cholesta-1,4,6-triene-3,24-dione (2).—(*a*) A solution of 3β-hydroxycholest-5-en-24-one (1)[26] (8.0 g) and dichlorodicyanobenzoquinone (15 g) in dioxan (120 ml) was refluxed for 14 h, cooled, filtered, diluted with methylene dichloride, and applied to a short column of alumina (80 g). Elution with methylene dichloride (600 ml) gave the *trienedione* (2) (4.1 g, 52%), m.p. 110—112 ° (from methanol), $\lambda_{max.}$ 223 (ε 12 000), 257 (9 200), and 301 nm (13 000), δ 0.80 (3H, s, 13-Me), 0.95 (3H, d, *J* 6 Hz, 20-Me), 1.10 (6H, d, *J* 7 Hz, 25-Me_2), 1.21 (3H, s, 10-Me), 6.0—6.2 (4H, m, 2-, 4-, 6-, and 7-H), and 7.1 (1H, d, *J* 10 Hz, 1-H) (Found: M^+, 394.2 888. $C_{27}H_{38}O_2$ requires *M*, 394.2874).

(*b*) A solution of cholest-4-ene-3,24-dione[32] (4.72 g) prepared by ozonolysis of fucostenone, and chloranil (4.7 g) in t-butyl alcohol (20 ml) was refluxed for 2 h, cooled, filtered, and evaporated to dryness. The residue was applied to a column of alumina (100 g) and eluted with methylene dichloride to give the crude 4,6-dienone (3.45 g), $\lambda_{max.}$ 287 nm. A solution of the dienone and dichlorodicyanobenzoquinone (3.0 g) in dioxan (30 ml) was refluxed for 14 h, cooled, filtered, and evaporated to dryness. The residue dissolved in methylene dichloride was filtered through a column of alumina (50 g) affording the trienedione (2) (2.31 g).

1α,2α-*Epoxycholesta-4,6-diene-3,24-dione* (3).—Hydrogen peroxide (30%; 5 ml) was added to a solution of the trienedione (2) (3.53 g) in methanol (100 ml), dioxan (50 ml), and tetrahydrofuran (20 ml) containing sodium hydroxide (80 mg), and the mixture was stirred at 15 °C overnight. The solution was diluted with ether and washed with brine. Drying (Na_2SO_4) and evaporation left a solid which was crystallised from acetone to give the *epoxide* (3) (2.41 g), m.p. 150—151.5°, $\lambda_{max.}$ 291 nm (ε 22 000), δ 0.78 (3H, s, 13-Me), 0.96 (3H, d, *J* 6 Hz, 20-Me), 1.08 (6H, d, *J* 7 Hz, 25-Me_2), 1.19 (3H, s, 10-Me), 3.40 (1H, dd, *J* 4 and 1.5 Hz, 2β-H), 3.58 (1H, d, *J* 4 Hz, 1β-H), 5.63 (1H, d, *J* 1.5 Hz, 4-H), and 6.10 (2H, s, 6- and 7-H) (Found: M^+, 410.2793. $C_{27}H_{38}O_3$ requires *M*, 410.2821).

1α,3β,24ξ-*Trihydroxycholest-5-ene* (4).—A four-necked flask was fitted with a sealed mechanical stirrer, a dropping funnel, a cold-finger filled with solid CO_2, and an inlet connected to an anhydrous ammonia source. Nitrogen was swept through the system for 10 min, and then ammonia (10 ml) was trapped in the flask. Lithium wire (150 mg) was cut into short pieces and added. After stirring for 10 min, the epoxide (3) (100 mg) in tetrahydrofuran (13 ml) was added dropwise during 20 min. The cooling bath was removed and the mixture was allowed to reflux for 20 min. The flask was dipped in a cooling bath and anhydrous ammonium chloride (1.5 g) was added during 2 h; the mixture turned white and pasty. Most of the ammonia was removed in a stream of nitrogen and the residue was diluted with ethyl acetate, washed with brine, and dried (Na_2SO_4). Evaporation left a white solid, which was applied to a column of silica gel (4 g). Elution with benzene–acetone (3 : 1) afforded the *triol* (4) (68 mg) as an amorphous powder, δ (C_5D_5N), 0.70 (3H, s, 13-Me), 3.3 (1H, m, 24-H, overlapped with OH), 3.83 (1H, m, 1β-H), and 4.05 (1H, m, 3α-H) (Found: M^+, 418.3428. $C_{27}H_{46}O_3$ requires *M*, 418.3449).

1α,3β,24ξ-*Triacetoxycholest-5-ene* (5).—The triol (4) (60 mg) was kept at 95 °C for 3.5 h with acetic anhydride (8 ml) and pyridine (25 ml). Work-up as usual gave the triacetate (5) (65 mg), an oil, δ 0.67 (3H, s, 13-Me), 2.02 (9H, s, 3 × OAc), 4.8 (2H, m, 3α- and 24-H), 5.05 (1H, m, 1β-H), and 5.6 (1H, m, 6-H), *m/e* 484 (M^+ — AcOH), 424 (M^+ — 2AcOH), and 364 (M^+ — 3AcOH).

1α,3β,24ξ-*Tribenzoyloxycholest-5-ene* (6).—The triol (4) (1.25 g) was kept at room temperature overnight with benzoylchloride (1.05 g) and pyridine (20 ml). After work-up in the usual manner, the product was chromatographed on a column of silica gel (60 g). Elution with benzene gave the tribenzoate (6) (250 mg), an oil, δ 0.65 (3H, s, 13-Me), 5.0 (1H, m, 24-H), 5.2 (1H, m, 3α-H), 5.4 (1H, m, 1β-H), 5.7 (1H, m, 6-H), and 7.4—8.2 (15H, m, Ph).

The 1α-*Hydroxy-3β,24ξ-dibenzoxycholest-5-enes* (7).—In the foregoing chromatography, further elution with benzene–ethyl acetate (200 : 1) afforded the 3β,24ξ[2]-*dibenzoate* (8) (596 mg), m.p. 168—169° (from methanol), δ 0.67 (3H, s, 13–Me), 3.91 (1H, m, 1β-H), 5.00 (1H, m, 24-H), 5.3 (1H, m, 3α-H), 5.65 (1H, m, 6-H), and 7.3—8.2 (10H, m, Ph) (Found: C, 78.6; H, 8.7. $C_{41}H_{54}O_5$ requires C, 78.55; H, 8.7%). Continued elution with the same solvent gave the 3β,24ξ[1]-*dibenzoate* (684 mg), m.p. 139.5—140.5° (from methanol), n.m.r. spectrum identical with that of the 24ξ[2]-isomer (Found: C, 78.4; H, 8.8%).

1α,3β,24ξ-*Trihydroxycholesta-5,7-diene* (8).—To a refluxing solution of the acetate (5) (301 mg) in n-hexane (4.5 ml), dibromodimethylhydantoin (92 mg) was added in one portion. Stirring under reflux was continued for 15 min. The mixture was cooled and the resulting imide was filtered off. Evaporation of the filtrate gave a pale yellow syrup (349 mg). The residue in xylene (2.5 ml) was added dropwise to a mixture of *s*-collidine (0.85 ml) and xylene (1.90 ml) at 165 °C, during 15 min. After heating for a further 10 min, the solution was cooled and the precipitate was filtered off. The filtrate was evaporated under vacuum and the residue was redissolved in ether. The solution was washed with N-hydrochloric acid and then with brine, dried (Na_2SO_4), and evaporated to give a pale orange oil (310 mg). U.v. analysis ($\lambda_{max.}$ 233, 241, 249, 272, 282, and 293 nm) showed the presence of 4,6- and 5,7-dienes in the ratio *ca.* 1 : 2. The mixture was dissolved in methanol (8 ml), benzene (9 ml), and methanolic 2N-potassium hydroxide (10 ml) and heated at 65 °C for 1 h. Extraction with ethyl acetate and the usual work-up gave an oil (256 mg). A repeated development of the product on a silver nitrate-impregnated silica gel plate with 6% methanol–chloroform showed two distinct u.v.-absorbing bands. The u.v. spectrum of the less polar fraction ($\lambda_{max.}$ 232, 240, and 249 nm) was characteristic of the 4,6-diene chromophore. Elution of the more polar band with ethyl acetate afforded the pure 5,7-*diene* (8) (85 mg), m.p. 102—103°, $\lambda_{max.}$ 271.5 (ε 11 000), 282 (12 000), and 294.5 nm (7 000), δ 0.63 (3H, s, 13-Me), 3.33 (1H, m, 24-H), 3.75 (1H, m, 1β-H), 4.06 (1H, m, 3α-H), and 5.5 (2H, AB-type q *J* 6 Hz, 6- and 7-H) (Found: M^+, 416.3357. $C_{27}H_{44}O_3$ requires *M*, 416.3293).

The 1α,3β,24ξ-*Trihydroxycholesta-5,7-dienes* (8).—The 3β,-24ξ[1]-dibenzoate (545 mg) was kept at 15 °C overnight with acetic anhydride (4 ml) and pyridine (4 ml). Work-up as usual gave the corresponding 1α-acetate (566 mg), δ 0.67 (3H, s, 13-Me), 2.06 (3H, s, Ac), 4.8—5.4 (3H, m, 1β-, 3α-, and 24-H), 5.55 (1H, m, 6-H), and 7.3—8.2 (10H, m, Ph). The acetate (545 mg) and *N*-bromosuccinimide (222 mg) in carbon tetrachloride (20 ml) were heated under reflux for

30 min. The precipitate was filtered off and the filtrate evaporated to dryness. The residue in xylene (2 ml) was added to a refluxing mixture of trimethyl phosphite (0.52 ml) and xylene (6 ml). After refluxing for 90 min the solution was evaporated under vacuum and the residue dissolved in chloroform (6 ml). A solution of 4-phenyl-1,2,4-triazoline-3,5-dione (290 mg) in chloroform (5 ml) was added until the pink colour persisted for 5 min. The solvent was evaporated off under vacuum and the residue was applied to a column of silica gel (20 g). Elution with benzene–ethyl acetate (25 : 1) afforded the adduct (129 mg), δ 2.06 (3H, s, Ac), 4.7—5.2 (3H, m, 1β-, 3α-, and 24-H), 6.41 (2H, AB-type q, J 8 Hz, 6- and 7-H), and 7.2—8.1 (15H, m, Ph). The adduct was refluxed with lithium aluminium hydride (200 mg) in tetrahydrofuran (15 ml) for 8 h. Work-up as usual and column chromatography on silica gel afforded an impure compound (25 mg). The u.v. spectrum showed $\lambda_{max.}$ 248 nm in addition to the expected 272, 282, and 292 nm. Final purification by preparative t.l.c. on silver nitrate-impregnated silica gel gave the 24ξ^1-5,7-diene (10 mg), m.p. 121—124°.

The 3β,24ξ^2-dibenzoate was converted into the 5,7-diene, m.p. 96—99°, according to the same procedures.

1α,24ξ-*Dihydroxycholecalciferol* (9).—A solution of the mixture of 5,7-dienes (8) (30 mg) in ether (500 ml) in a quartz apparatus cooled in an ice-bath was agitated by a stream of argon for 10 min and then irradiated with a medium-pressure mercury lamp (Hanovia 654A36; 200 W) immersed in the vessel for 5.5 min. Most of the ether was evaporated off and the residue dissolved in benzene (180 ml) was refluxed for 2 h under argon. The solvent was evaporated off and the residue was applied to a silver nitrate-impregnated silica gel plate. Development with 6% methanol–chloroform (3 times) revealed three u.v.-absorbing bands. The least polar band was scraped off and eluted with ethyl acetate to give the vitamin (9) (3.7 mg), m.p. 84—85°, $\lambda_{max.}$ 266 nm (ε 17 000), δ [$(CD_3)_2CO$], 0.57 (3H, s, 13-Me), 0.87 (6H, d, J 7 Hz, 25-Me_2), 0.96 (3H, d, J 5 Hz, 20-Me), 3.19 (1H, m, 24-H), 4.15 (1H, m, 1β-H), 4.36 (1H, m, 3α-H), 4.85br (1H, s) and 5.30br (1H, s) (19-H_2), and 6.05 (1H, d, J_{AB} 11 Hz) and 6.26 (1H, d, J_{AB} 11 Hz) (6- and 7-H), *m/e* 416 (M^+), 398 ($M - H_2O$), 380 ($M - 2H_2O$), 269, 251, 134, and 105.

The individual 1α,24ξ^1- *and* 1α,24ξ^2-*dihydroxycholecalciferols* were similarly obtained from the 24ξ^1- and 24ξ^2-5,7-dienes. Their spectral (u.v., n.m.r., and mass) properties were practically indistinguishable from those of the 24ξ-mixture.

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