Synthesis of Active Forms of Vitamin D. II.1) Synthesis of 1α-Hydroxycholesterol2)

In our synthetic studies of 1α,25-dihydroxycholecalciferol, a biologically active form of vitamin D₃, it seemed to us of essential need to carry out model experiments which will pave an unequivocal route to 1α-hydroxycholesterol. Our final product (Va) was found to have different mp and [α]₀ from the reported for "1α-hydroxycholesterol," probably due to an erroneous assignment of the structure.6)

Epoxidation of 6β-acetoxy-5α-cholesten-1-en-3-one (I)3) with 35% H₂O₂ in 5% NaOH/CHCl₃/Methanol (20°, 1 hr) gave 1α,2α-epoxide (II) in 68% yield, mp 132—133.5°, nmr (CDCl₃) δ, 1.03 (3H, s), 3.24 (1H, d, J=4 Hz) and 3.48 ppm (1H, d, J=4 Hz). Reaction of II with NaBH₄ in MeOH/ether (20°, 30 min) yielded a mixture of epimeric alcohols (IIIa) (the ratio of 3β to 3α-ol, 4:1, estimated from the ratio of isolated V to VI, vide infra), which was, without separation, successively treated with 5% NaOH in aq. MeOH (60°, 1.5 hr), chromatographed on silica gel and with a half equivalent of Ac₂O in pyridine/benzene (20°, 2 hr). By chromatography of the product on silica gel, 3β-acetate (IIIb) mp 157—159° was obtained in 24% overall yield from II. Nuclear magnetic resonance (NMR) signal of C₃-H and C₂-H appeared at 3.02 ppm (2H) as a singlet, supporting the configuration of 1, 2 and 3 positions in IIIb (the dihedral angle between 3α-H and 2α-H is approximately 90°).

Dehydration of 3β-acetate (IIIb) was effected with POCl₃ in pyridine (20°, 2 hr) to give the olefine (IV), mp 106—108° in 75% yield. Reduction of IV with LiAlH₄ in refluxing tetrahydrofuran (3.5 hr) afforded 1α-hydroxycholesterol (Va) in 84% yield, mp 152—155° (from n-hexane/acetone), [α]₀ = 39°, NMR (CDCl₃), δ, 1.01 (3H, s), 3.8 (1H, m), 3.9 (1H, m) and 5.55 ppm (1H, m). M⁺ 402.346 (calculated for C₃₇H₅₆O₂: 402.349).

The structure of Va was further confirmed by converting into the known 1α,3β-dihydroxycholestenane, identified by direct comparison (MP, IR, NMR, TLC, and GLC) with an authentic sample prepared by the method of Striebel and Tamm.7)

Alternatively and more conveniently, 1α-hydroxycholesterol (Va) was synthesized from II in an overall yield of 30%, without purification of intermediates, as follows:

The crude product (IIIa) (260 mg) was treated with dihydropyran in CH₂Cl₂ in the presence of p-TsOH (20°, 2 min) to give tetrahydroxypropyl ether, which was transformed into the alcohol (IIIc) by refluxing (1 hr) with 4% NaOH/MeOH. Dehydration with POCl₃ and reduction with LiAlH₄ were performed as described above for IIIb, affording the hydroxy pyranyl ether (Vb and its 3α-epimer). Treatment with HCl/MeOH (20°, 30 min) to remove the THP group and final purification by column chromatography on silica gel gave 1α-hydroxycholesterol (Va) (87 mg) and cholest-5-ene-1α,3α-diol (VI) (21 mg), mp, 201—206°, [α]₀ = 30°, NMR (CDCl₃) δ, 0.98 (3H, s), 3.8 (1H, m) and 5.6 ppm (1H, m).

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2) Presented at the 165 th National Meeting of American Chemical Society, Dallas, April, 1973.
3) See accompanying paper.
4) See for example footnote 3) in Part I of this series.
5) B. Pelc and E. Kodicke, J. Chem. Soc. (C), 1970, 1624. We could not reproduce their results when tracing their procedures.
6) Dr. C. Kaneko, et al (Tokyo Medical and Dental University) independently obtained 1α-hydroxycholesterol whose physical data were consistent with ours (The 93 rd Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1973).
Synthesis of Active Forms of Vitamin D. III. 1) Synthesis of 1α,25-Dihydroxycholesterol 2)

1α,25-Dihydroxycholecalciferol is a metabolite of vitamin D₃ with a higher biological activity than the parent vitamin, 3) and hence stimulated the interest of several research groups in finding a synthetic route to obtain it. The goal of this synthesis is 1α,25-dihydroxycholesterol, since it should be easily convertible to 1α,25-dihydroxycholecalciferol as recently verified by Semmler, et al. 4)

Saponification of 25-hydroxycholesterol 3-acetate (Ia) 5) followed by treatment with dihydropyran in CH₂Cl₂ in the presence of p-TsOH (20°, 30 min) gave dipyranyl ether (Ib). Hydroboration 6) of Ib was carried out by treatment with B₂H₆ in tetrahydrofuran (15°, 2 hr)

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2) Presented at the 165th National Meeting of American Chemical Society, Dallas, April, 1973.