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Synthesis of Active Forms of Vitamin D. II.[1] Synthesis of 1α-Hydroxycholesterol[2]

In our synthetic studies[3] of 1α,25-dihydroxycholecalciferol, a biologically active form of vitamin D_3,[4] 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 $[\alpha]_D$ from the reported[5] for "1α-hydroxycholesterol," probably due to an erroneous assignment of the structure.[6]

Epoxidation of 6β-acetoxy-5α-cholest-1-en-3-one (I)[5] with 35% H_2O_2 in 5% NaOH/$CHCl_3$/MeOH (20°, 1 hr) gave 1α,2α-epoxide (II) in 68% yield, mp 132—133.5°, nmr ($CDCl_3$) 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 $NaBH_4$ 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 Ac_2O 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 C_1-H and C_2-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 2β-H is approximately 90°).

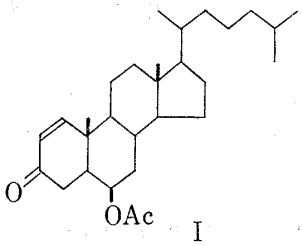
Dehydration of 3β-acetate (IIIb) was effected with $POCl_3$ in pyridine (20°, 2 hr) to give the olefine (IV), mp 106—108° in 75% yield. Reduction of IV with $LiAlH_4$ in refluxing tetrahydrofuran (3.5 hr) afforded 1α-hydroxycholesterol (Va) in 84% yield, mp 152—155° (from *n*-hexane/acetone), $[\alpha]_D$ −39°, NMR ($CDCl_3$), δ, 1.01 (3H, s), 3.8 (1H, m), 3.9 (1H, m) and 5.55 ppm (1H, m). M^+ 402.346 (calculated for $C_{27}H_{46}O_2$: 402.349).

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

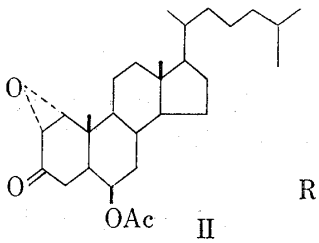
Alternatively and more conveniently, 1α-hydroxycholesterol (Va) was synthesized from II in an overall yield of 30%, without purification of intermediates, as follows:

The crude product (IIIa) (260 mg) was treated with dihydropyran in CH_2Cl_2 in the presence on *p*-TsOH (20°, 2 min) to give tetrahydropyranyl ehter, which was transformed into the alcohol (IIIc) by refluxing (1 hr) with 4% NaOH/MeOH. Dehydration with $POCl_3$ and reduction with $LiAlH_4$ 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°, $[\alpha]_D$ −30°, NMR ($CDCl_3$) δ, 0.98 (3H, s), 3.8 (1H, m) and 5.6 ppm (1H, m).

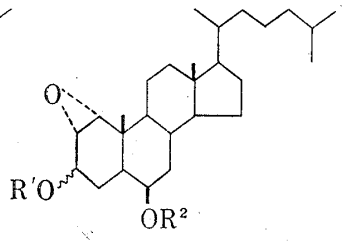
1) Part I: M. Morisaki, J. Rubio-Lightbourn and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 457 (1973). This is also Part VII in the series of "Studies on Steroids" Part VI: H. Ohtaka, M. Morisaki and N. Ikekawa, *J. Org. Chem.*, **38**, 1688 (1973).
2) Presented at the 165 th National Meeting 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. Kodicek, *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).
7) P. Striebel and C. Tamm, *Helv. Chim. Acta*, **37**, 1094 (1954).



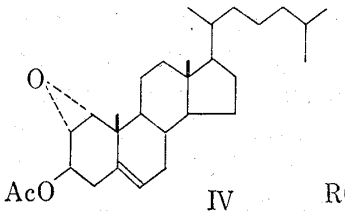
I



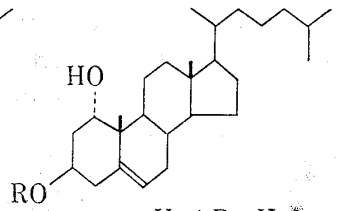
II



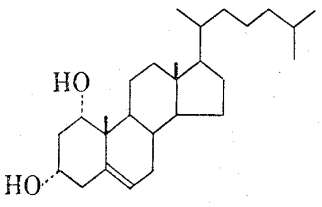
IIIa : R^1=H, R^2=Ac
IIIb : R^1=Ac, R^2=H
IIIc : R^1=THP, R^2=H



IV



Va : R=H
Vb : R=THP



VI

Laboratory of Chemistry for Natural Products,
Tokyo Institute of Technology
Ohokayama, Meguro-ku, Tokyo

MASUO MORISAKI
KIYOSHI BANNAI
NOBUO IKEKAWA

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Synthesis of Active Forms of Vitamin D. III.[1] Synthesis of 1α,25-Dihydroxycholesterol[2]

1α,25-Dihydroxycholecalciferol is a metabolite of vitamin D_3 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 CH_2Cl_2 in the presence of *p*-TsOH (20°, 30 min) gave dipyranyl ether (Ib). Hydroboration[6] of Ib was carried out by treatment with B_2H_6 in tetrahydrofuran (15°, 2 hr)

1) Part II: M. Morisaki, K. Bannai and N. Ikekawa, This is also Part VIII in the series of "Studies on Steroids," Part VII: *Chem. Pharm. Bull.* (Tokyo), **21**, 1853 (1973).
2) Presented at the 165 th National Meeting of American Chemical Society, Dallas, April, 1973.
3) J. Omdahl, M. Holick, T. Suda, Y. Tanaka and H.F. DeLuca, *Bichemistry*, **10**, 2935 (1971); M.F. Holick, M. Garabedian and H.F. DeLuca, *Science*, **176**, 1146 (1972); Y. Tanaka, H. Frank and H.F. DeLuca, *J. Nutrition*, **102**, 1569 (1972).
4) E.J. Semmler, J.F. Holick, H.K. Schnoes and H.F. DeLuca, *Tetrahedron Letters*, **1972** 4147.
5) M. Morisaki, J. Rubio-Lightbourn and N. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **21**, 457 (1973).
6) *cf.* S. Wolfe, N. Nussim, Y. Mazur and F. Sondheimer *J. Org. Chem.*, **24**, 1034 (1959).