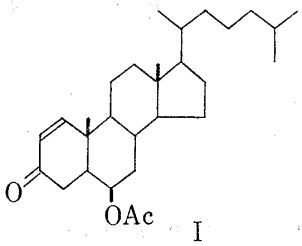
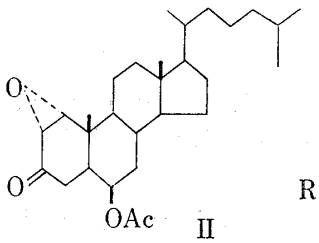



I

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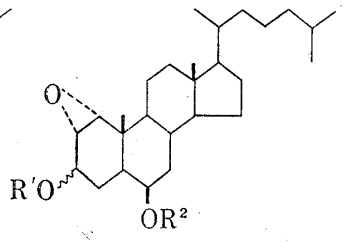
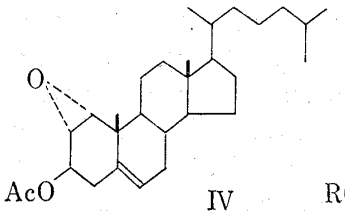
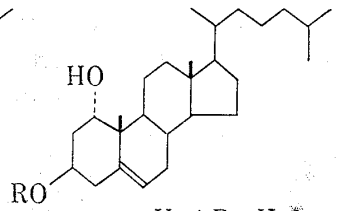


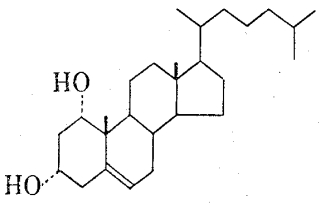

IIIa : $R^1$=H, $R^2$=Ac
IIIb : $R^1$=Ac, $R^2$=H
IIIc : $R^1$=THP, $R^2$=H




IV




Va : R=H
Vb : R=THP




VI

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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]

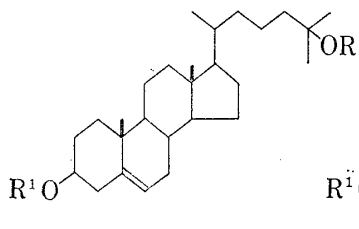
Saponification of 25-hydroxycholesterol 3-acetate (Ia)[5] followed by treatment with dihydropyran in $CH_2Cl_2$ in the presence of *p*-TsOH (20°, 30 min) gave dipyranyl ether (Ib). Hydroboration[6] of Ib was carried out by treatment with $B_2H_6$ in tetrahydrofuran (15°, 2 hr)

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).

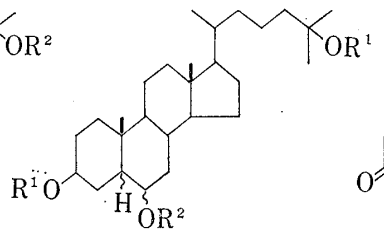
followed by 30% $H_2O_2$ in 3N NaOH, to give the alcohol (IIa). Gas–liquid chromatography (GLC) analysis as its trimethylsilyl ether (IIb) indicated to be a 5:1 mixture of 5α,6α- and 5β,6β-isomers. Oxidation of IIa with $CrO_3$–pyridine in $CH_2Cl_2$[7] (20°, 1 hr) gave a ketone which was reconverted into alcohol (IIa) by treatment with $NaBH_4$ in MeOH/ether (20°, 1 hr). The predominating (80% from GLC analysis[8]) alcohol in the crude product was predicted to have 5α-H,6β-ol configuration from the well known[9] stereoselectivity in reduction of 6-keto-5α-steroids. Acetylation of IIa with $Ac_2O$–pyridine (75°, 1.5 hr) and removal of the THP group with HCl/MeOH (0°, overnight) gave IIc, which was oxidized with $CrO_3$–pyridine in $CH_2Cl_2$[7] (20°, 15 min) to afford, after cromatography on silica gel, 6β,25-dihydroxy-5α-cholestan-3-one 6-acetate (III), mp 136—138°, NMR ($CDCl_3$), δ, 1.18 (3H, s), 1.20 (6H, s) and 4.88 ppm (1H, m) in 52% yield from Ia, without purification of intermediates during these 7 steps. The expected AB *trans* ring junction of III was evidenced by (+)-Cotton effect on its ORD curve.

Introduction of $\Delta^{1(2)}$-double bond needed for the elaboration of 1α-hydroxy group was achieved in 60% yield by bromination with 1.1 equivalent of bromine in AcOH in the presence of a catalytic amount of 30% HBr in AcOH (20°, 10 min) followed by dehydrobromination with $CaCO_3$ in dimethylformamide (reflux, 1 hr). However, in this process, a concomitant partial dehydration of C-25 hydroxy group was occurred to give a mixture of $\Delta^{24(25)}$-, and $\Delta^{25(26)}$-compounds (IV),[10] NMR ($CDCl_3$), δ, 1.17 (3H, s), 1.60 (3H, s), 1.67 (3H, s), 2.04 (3H, s), 4.65 and 5.0 (m), 5.80 (1H, d, $J$=10 Hz) and 7.00 ppm (1H, d, $J$=10 Hz).

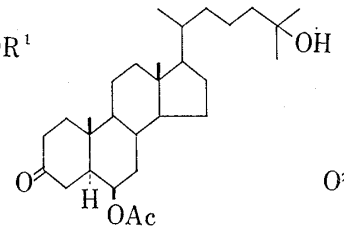
Conversion of IV to 1α,3β-dihydroxy-$\Delta^5$-derivative (VII) was performed in the same manner as described for 6β-acetoxycholesten-3-one in a preceding paper,[1] leading successively to epoxy ketone (V), mp 143—145° (45%), NMR ($CDCl_3$), δ, 3.23 (1H, d, $J$=4 Hz) and 3.47 ppm (1H, d, $J$=4 Hz), alcohol (VIa) (60%), NMR ($CDCl_3$) δ, 3.01 (2H, s) and 4.0 ppm (1H, m), THP ether (VIb) (80%), and finally VIIa, mp 132—133° (80%).



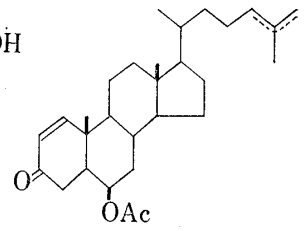
Ia: $R^1$=Ac, $R^2$=H
Ib: $R^1$=$R^2$=THP



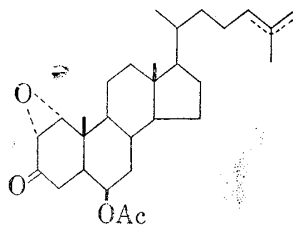
IIa: $R^1$=THP, $R^2$=H
IIb: $R^1$=$R^2$=TMS
IIc: $R^1$=H, $R^2$=Ac



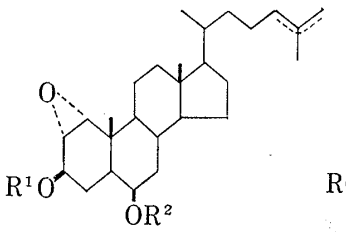
III



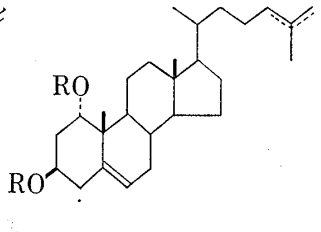
IV



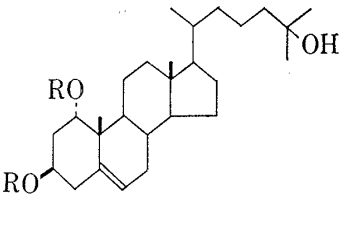
V



VIa: $R^1$=H, $R^2$=Ac
VIb: $R^1$=THP, $R^2$=H



VIIa: R=H
VIIb: R=Ac



VIIIa: R=Ac
VIIIb: R=H

7) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
8) Relative retention time of 5β,6β-, 5α,6α- and 5α,6β-isomers when analyzed as their TMS ether (1.5% OV-17, at 253°) were 6.5, 10.1 and 8.5 min respectively.
9) D.M.S. Wheeler and M.M. Wheeler in, "Organic Reactions in Steroid Chemistry," Vol. I, J. Fried & J.A. Edwards, Ed., Reinhold, New York, 1972, p. 61.
10) About one third of 25-hydroxy analogue contained in the crude product was converted to IV by treatment with $POCl_3$ in pyridine (20°, 1 hr).

Recovering of 25-hydroxy group[11] was accomplished by treatment of diacetate (VIIb) with Hg $(OAc)_2$ in aq. tetrahydrofuran (0°, 3 hr and then 20°, 4 hr), followed by addition of 1 M NaOH and reduction with $NaBH_4$ to give, in 67% yield, 1α,25-dihydroxycholesterol 1,3-diacetate (VIIIa), NMR ($CDCl_3$), δ, 1.08 (3H, s), 1.20 (6H, s), 2.01 (3H, s), 2.05 (3H, s), 4.9 (1H, m), 5.05 (1H, m) and 5.5 ppm (1H, m).

Synthesis of 1α,25-dihydroxycholesterol was completed when diacetate (VIIIa) was hydrolized with 30% NaOH in MeOH/benzene/$H_2O$ (reflux, 2 hr), mp 161—163° $[\alpha]_D$ −29°. $M^+$ 418.341 (calculated for $C_{27}H_{46}O_3$: 418.344).

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11) A model experiment showed that oxymercuration-demercuration reaction of a mixture of $\Delta^{24(25)}$-, and $\Delta^{25(26)}$-cholest-5-en-3β-OAc yielded the single product, 25-hydroxycholesterol 3-acetate.