Communications to the Editor

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SYNTHETIC STUDIES OF VITAMIN D ANALOGUES. VII.[1] SYNTHESIS OF 20-OXA-21-NORVITAMIN D_3 ANALOGUES

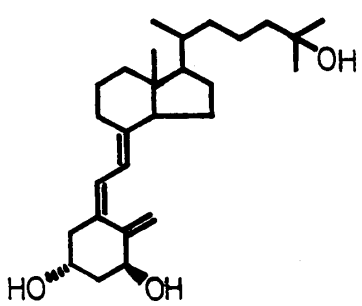
Noboru Kubodera,* Katsuhito Miyamoto, Kiyoshige Ochi and Isao Matsunaga

New Drug Research Laboratories, Chugai Pharmaceutical Co., Ltd., 41-8, Takada 3 chome, Toshima-ku, Tokyo 171, Japan

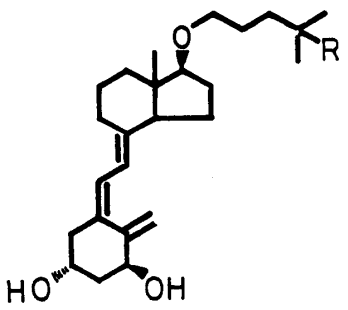
The synthesis of two vitamin D_3 analogues, 1α,25-dihydroxy-20-oxa-21-norvitamin D_3 (2) and 1α-hydroxy-20-oxa-21-norvitamin D_3 (3) from dehydroepiandrosterone (4) is described.

KEYWORDS——dehydroepiandrosterone: vitamin D_3 analogue; 1α,25-dihydroxy-20-oxa-21-norvitamin D_3; 1α-hydroxy-20-oxa-21-norvitamin D_3; 1-chloro-4,4-ethylenedioxypentane; vitamin D_3 synthesis

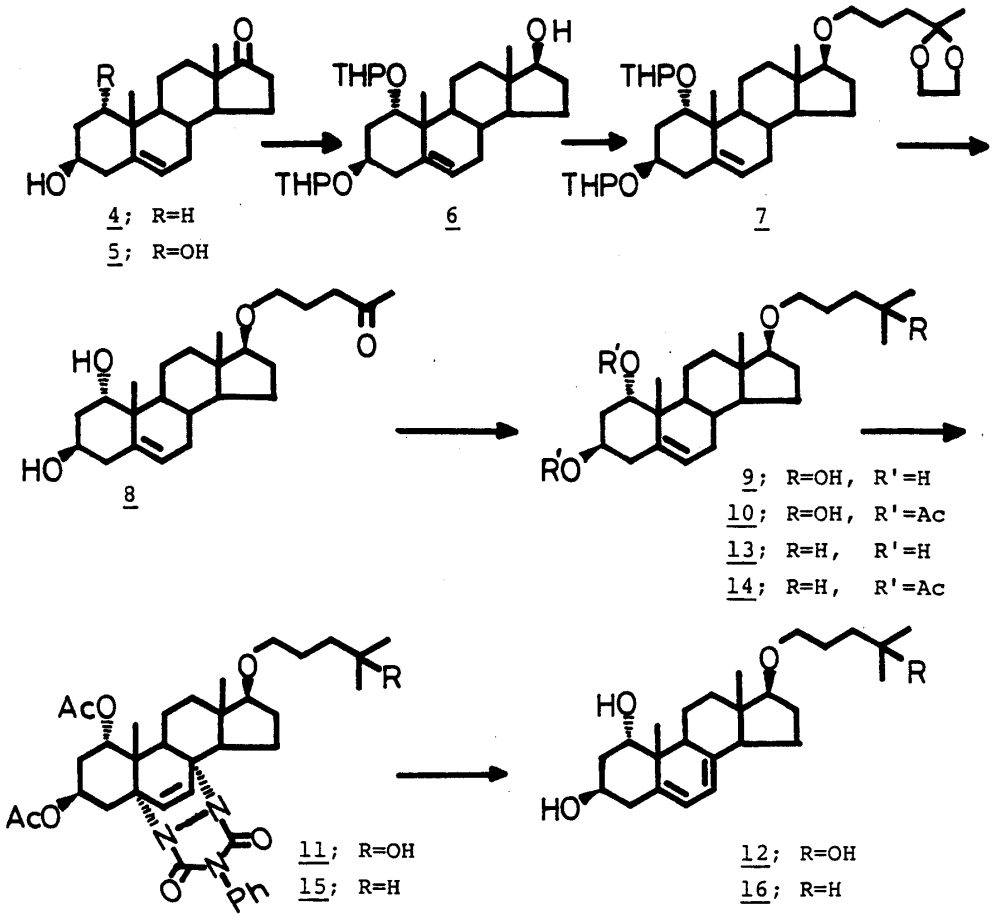
There has been increasing interest in the synthesis of vitamin D_3 analogues since 1α,25-dihydroxyvitamin D_3 (1) [1α,25-$(OH)_2$-D_3] was shown to have a differentiation-inducing effect on myeloid leukemia cells in addition to its regulatory effect on calcium and phosphorus metabolism.[2] In an attempt to separate these types of physiological action, we have undertaken the synthesis of vitamin D_3 analogues having an oxygen atom in the side chain skeleton. Only a few vitamin D_3 analogues containing heteroatoms in the side chain were prepared,[3,4] and the details of their biological activities are not available. This paper deals with the synthesis of 1α,25-dihydroxy-20-oxa-21-norvitamin D_3 (2) and 1α-hydroxy-20-oxa-21-norvitamin D_3 (3) from dehydroepiandrosterone (4), and with the preliminary studies of their biological activities.



1 : 1α,25-OH-D_3



2 ; R = OH
3 ; R = H



The ketodiol (5), prepared from 4 by microbiological 1α-hydroxylation,[5] was converted to the 17β-alcohol (6)[6a] in 42% yield via bis-tetrahydropyranyl ether formation followed by reduction with $NaBH_4$ in EtOH at room temperature for 2 h. Alkylation[7] of 6 with 1-chloro-4,4-ethylenedioxypentane[8] in the presence of NaH in boiling xylene for 20 h gave the ether (7)[6b] in 66% yield. Then 7 was hydrolyzed to the 24-keto-diol (8)[6c] in 78% yield upon treatment with Amberlyst-15 in MeOH at room temperature for 15 h. Addition of 8 to excess MeMgBr in THF at -10°C during 0.5 h afforded the triol (9)[6d] in 66% yield. The secondary hydroxyl groups in 9 were acetylated and the resulting diacetate (10)[6e] was transformed into the 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) adduct (11)[6f] in 32% overall yield by the usual 3-step procedure: i) bromination at the 7-position (NBS, $NaHCO_3$, hexane, reflux, 1 h); ii) dehydrobromination (γ-collidine, xylene, reflux, 1.5 h); and iii) addition of PTAD[9] (CH_2Cl_2, room temperature, 1 h). Treatment[9] of 11 with $LiAlH_4$ in refluxing THF for 1 h afforded the 5,7-diene (12)[6g] in 48% yield. Subsequent irradiation[10] of 12 in EtOH at 0°C under argon atmosphere using a high pressure mercury lamp (200 W, Vycor filter), followed by thermal isomerization in boiling THF for 1.5 h gave 1α,25-dihydroxy-20-oxa-21-norvitamin D_3 (2)[6h] in 12% yield after purification by means of Sephadex LH-20 column chromatography with $CHCl_3$-hexane (13:7).

Another analogue, 1α-hydroxy-20-oxa-21-norvitamin D_3 (3), was prepared in a similar manner. The alcohol 6 was converted to the diol ether (13)[6i] via alkylation with 1-bromo-4-methylpentane (72% yield) followed by hydrolysis of the tetrahydropyranyl ether groups (73% yield). The diacetate (14)[6j] was transformed into the PTAD adduct (15)[6k], in 41% yield by the same procedure as in the preparation of 11. Treatment of 15 with $LiAlH_4$ afforded the 5,7-diene (16)[6l] in 41% yield, which was subjected to the irradiation-thermal isomerization sequence to give 3[6m] in 12% overall yield.

Some preliminary studies showed that 2 and 3 have interesting biological properties. In in vitro experiments exploring the inducing effect of differentiation of human myeloid leukemia cells (HL-60) into macrophages,[11] 2 and 3 were respectively proved to be as effective as 1α,25-$(OH)_2$-D_3 and 3 1α-hydroxyvitamin D_3 (1α-OH-D_3). On the other hand, in vitro measurement of binding affinity with chick intestinal cytosolic receptor[12] disclosed that 2 and 3 have only one 1,000th as much affinity as 1α,25-$(OH)_2$-D_3 and 1α-OH-D_3 and application of 2 to rats deficient in vitamin D showed no effect on intestinal calcium transportation and bone calcium mobilization at a dose of 125 μg/kg (iv). Pharmacological studies are now under investigation.

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6) a) 6: colorless foam softening at 86-93°C; IR ν_{max}^{KBr} cm^{-1}: 3460, 1025; NMR ($CDCl_3$) δ: 0.76(3H,s), 1.00(1.3H,s), 1.01(1.7H,s), 4.5-4.8(2H,br), 5.3-5.5(1H,br).

b) 7: pale yellow oil; IR ν_{max}^{Nujol} cm^{-1}: 1030; NMR($CDCl_3$) δ: 0.77(3H,s), 1.00(1.3H,s), 1.02(1.7H,s), 1.31(3H,s), 3.45(2H,brt, J=6Hz), 3.91(4H,s) 4.5-4.9(2H,s), 5.4-5.6(1H,br); MS m/e: 602(M^+), 85(100%).

c) 8: colorless prisms; mp 96-97°C; IR ν_{max}^{Nujol} cm^{-1}: 3350, 1710; NMR($CDCl_3$) δ: 0.75(3H,s), 1.02(3H,s), 2.00 (2H,s, exchanged with D_2O), 2.13(3H,s), 3.1-4.0(3H,br), 3.42(2H,t, J=6Hz), 5.45-5.65(1H,br); MS m/e: 390(M^+), 85(100%).

d) 9: colorless powder; mp 70-72°C; IR ν_{max}^{Nujol} cm^{-1}: 3400; NMR($CDCl_3$) δ: 0.78(3H,s), 1.03(3H,s), 3.47(2H,br t, J=6Hz), 5.4-5.6(1H,br); MS m/e 406(M^+), 83(100%).

e) 10: colorless oil; IR ν_{max}^{neat} cm^{-1}: 3450, 1730, 1240; NMR($CDCl_3$) δ: 0.75(3H,s), 1.08(3H,s), 1.20(6H,s), 1.98(3H,s), 2.01(3H,s), 2.70(1H,s, exchanged with D_2O), 3.1-3.6(3H,br), 4.7-5.1(2H,br), 5.4-5.6(1H,br); MS m/e: 472(M^+-H_2O), 118(100%).

f) 11: colorless powder; mp 115-117°C; IR ν_{max}^{neat} cm^{-1}: 3475, 1740, 1690, 1240; NMR($CDCl_3$) δ: 0.91(3H,s), 1.06(3H,s), 1.21(6H,s), 2.00(3H,s), 2.01(3H,s), 3.1-3.7(3H,br), 5.0-5.2(1H,br), 5.6-6.0(1H,m), 6.29(1H,d, J=8Hz), 6.49(1H,d, J=8Hz), 7.2-7.6(5H,m); MS m/e: 488(M^+-PTAD), 177(100%).

g) 12: colorless foam; IR ν_{max}^{neat} cm^{-1}: 3375; NMR($CDCl_3$) δ: 0.71(3H,s), 0.93(3H,s), 1.20(6H,s), 3.3-3.9(5H,br), 5.2-5.5(1H,br), 5.69(1H, br d, J=6Hz); UV λ_{max}^{EtOH} nm: 292.5, 281, 270.

h) 2: colorless crystals; NMR ($CDCl_3$) δ: 0.63(3H,s), 1.23 (6H,s), 3.51(3H,m), 4.17-4.29(1H,m), 4.34-4.49(1H,m), 4.98(1H,t, J=1.6Hz), 5.31(1H,t, J=1.6Hz), 5.99(1H,d, J=12.0Hz), 6.36(1H,d, J=12.0Hz); MS m/e: 404(M^+), 83(100%); UV λ_{max}^{EtOH} nm: 262, λ_{min}^{EtOH} nm: 227; α_D^{24} -44.6° (c=0.56, EtOH).

i) 13: colorless prisms; mp 129-131°C; IR ν_{max}^{Nujol} cm^{-1}: 3350; NMR($CDCl_3$) δ: 0.77(3H,s), 0.87(6H,d, J=6Hz), 1.03(3H,s), 2.55(2H,br, exchanged with D_2O), 3.41(2H,t, J=6Hz), 3.6-4.3(3H,br), 5.4-5.7(1H,br); MS m/e: 390(M^+), 372(100%).

j) 14: colorless foam; IR ν_{max}^{neat} cm^{-1}: 1740, 1240; NMR($CDCl_3$) δ: 0.76(3H,s), 0.87(6H,d, J=6Hz), 1.09(3H,s), 2.03(3H,s), 2.06(3H,s), 3.2-3.6(1H,br), 3.42(2H,t, J=6Hz), 4.6-5.2(2H,m), 5.4-5.7(1H,br); MS m/e: 474(M^+), 118(100%).

k) 15: colorless powder; mp 94-97°C; IR ν_{max}^{Nujol} cm^{-1}; 1740, 1690, 1230; NMR($CDCl_3$) δ: 0.87(6H,d, J=6Hz), 0.90(3H,s), 1.06(3H,s), 2.00(3H,s), 2.02(3H,s), 3.1-3.5(1H,br), 3.51(2H,t, J=6Hz), 5.0-5.2(1H,br), 5.6-6.0(1H,m), 6.27(1H,d, J=8Hz), 6.47(1H,d, J=8Hz), 7.2-7.6(5H,m); MS m/e: 472(M^+-PTAD), 352(100%).

l) 16: colorless powder; mp 87-90°C; IR ν_{max}^{Nujol} cm^{-1}: 3375; NMR($CDCl_3$) δ: 0.70(3H,s), 0.89(6H,d, J=6Hz), 0.92(3H,s), 3.45(2H,t, J=6Hz), 3.7-4.2(3H,br), 5.2-5.5(1H,br), 5.68(1H,br d, J=6Hz); MS m/e: 388(M^+), 134(100%); UV λ_{min}^{EtOH} nm: 292.5, 281, 270.

m) 3: colorless crystals; NMR($CDCl_3$) δ; 0.62(3H,s), 0.86(3H,d, J=0.8Hz), 0.89(3H,d, J=0.8Hz), 3.35-3.56(3H,m), 4.15-4.32(1H,m), 4.38-4.51(1H,m), 5.00(1H,t, J=1.6Hz), 5.32(1H,t, J=1.6Hz), 6.00(1H,d, J=12.0Hz), 6.38(1H,d, J=12.0Hz); MS m/e: 388(M^+), 134(100%); UV λ_{max}^{EtOH} nm: 262, λ_{min}^{EtOH} nm: 227, $[\alpha]_D^{24}$ -30.2° (c=0.86, EtOH).

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