SYNTHESIS OF 24-DEHYDROCHOLECALCIFEROL

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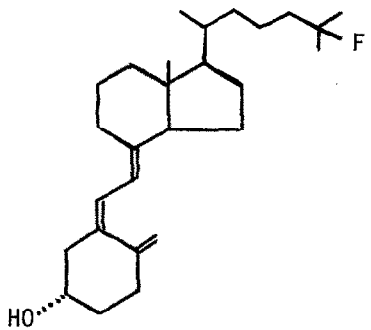
ABSTRACT

This paper describes the synthesis of 24-dehydrocholecalciferol from 5,7-cholestadiene-3β,25-diol 3-acetate.

In connection with our synthetic approach to 25-fluorocholecalciferol (1) (1), the ready availability of 5,7-cholestadiene-3β,25-diol 3-acetate (2) suggested the possibility of the synthesis of 24-dehydrocholecalciferol (3). Although J. P. Moreau, et al. (2) reported the use of methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt (4) for the dehydration of 2 without disturbing the homoannular diene system, the method appeared to be non-regiospecific, giving 24- and 25-olefinic derivatives in 1:1 ratio. We report a three-step synthesis of 3 directed toward both the regiospecific dehydration of the 25-hydroxyl group and also the preservation of the homodiene system in ring B of 2 giving 5,7, 24-cholestatrien -3β-ol (5).



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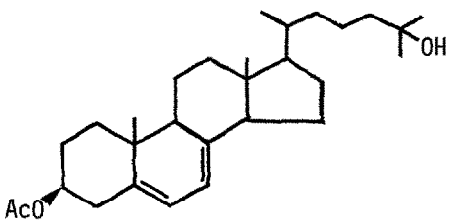

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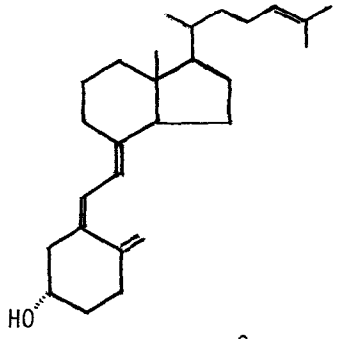

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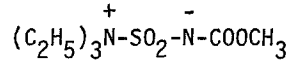

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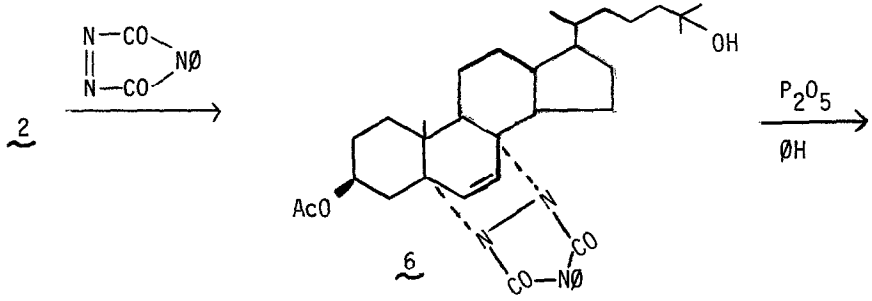
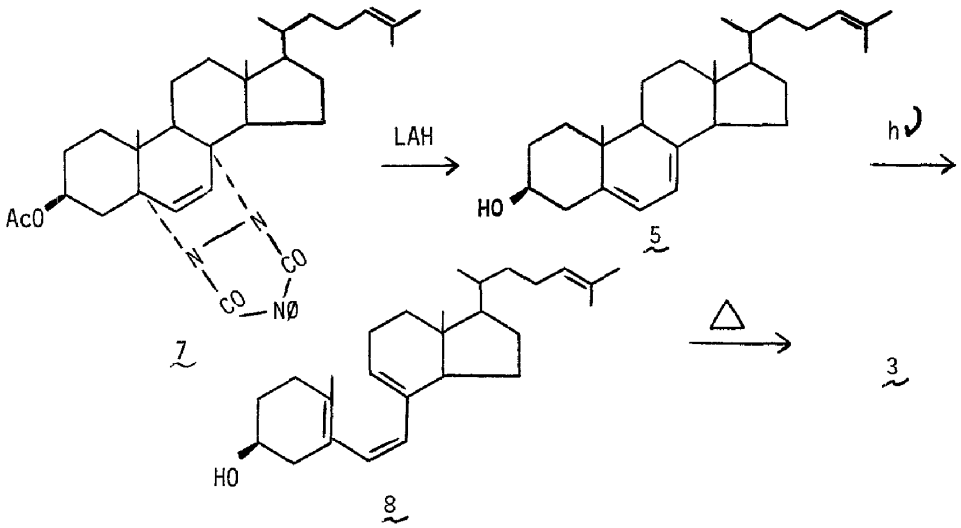
The homodiene system of compound 2 was protected as the 1,4-cycloadduct 6 by treating with 4-phenyl-1,2,4-triazoline-3,5-dione (3). Dehydration of 6 with anhydrous phosphorous pentoxide in benzene (4) at 30 to 35° gave the Δ^{24}-cycloadduct 7 in 80% yield as indicated by the presence of one vinyl proton as a triplet at 5.07 ppm (NMR). The homodiene moiety was then regenerated by refluxing 7 with lithium aluminum hydride in tetrahydrofuran to give 5 in 70% yield.

These results contrast with our earlier attempts to dehydrate 2 with phosphorous pentoxide in benzene or with phosphorous oxychloride in pyridine which resulted in the complete loss of homodiene moiety. Treatment of the Diels-Alder adduct 6 with phosphorous oxychloride in pyridine in the cold resulted in non-regiospecific dehydration.

Conversion of 5 into the vitamin 3 was carried out by established procedures (5).





Photolysis of an ether solution of 5 under nitrogen in a quartz cell at 0 to 5° for 9 min with a 450-W Hanovia lamp resulted in ca. 50% conversion. Purification of the reaction mixture via low temperature preparative tlc afforded 24-dehydroprevitamin D_3 (8) in 27% yield. Thermal isomerization of 8 in refluxing ethanol resulted in a 3:1 mixture of the vitamin 3 and the previtamin 8, from which 3 was isolated as a glass in 62% yield.

Experimental

General - All melting points were determined on a Thomas Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 237B or 267 spectrophotometer as Nujol mulls. Ultra violet spectra were taken on a Perkin Elmer 202 spectrophotometer. Proton nuclear magnetic resonance spectra were recorded on a Varian T-60 or T-60A spectrometer with Me_4Si as an internal standard. Mass spectra were determined on an LKB-9000 spectrometer.

4-Phenyl-1,2,4-triazoline-3,5-dione adduct (6) of 5,7-cholestadiene-3β, 25-diol 3-acetate:

To a solution of compound 2 (1.15 g, 26 mmole) in methylene chloride (30 ml) was added 4-phenyl-1,2,4-triazoline-3,5-dione (0.49 g, 28 mmole) in portions. After the addition was completed, the reaction mixture was concentrated to dryness and the residue was triturated with ether. The crystals collected were redissolved in methylene chloride and evaporated

to dryness. The ether trituration was repeated to give desired 6 (1.55 g, 87% based on 1 mole Et_2O solvation) : mp 161.5 - 162.5°; ir (nujol) νmax 3500, 1760, 1720 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 0.78 (s, 3H, 18-Me), 0.97 (s, 3H, 19-Me), 1.20 (s, 6H, 26, 27-Me's), 2.00 (s, 3H, CH_3CO), 3.21 (d of d, 1H, C-9-H), 5.4 (m, 1H, C-3-H), 6.16 and 6.40 (ABq, 2H, J = 9 Hz, C-6, 7-H's) and 7.33 ppm (s, 5H, ArH); mass m/e 617 (M^+), 599 ($M^+ - H_2O$), 382 (M^+-AcOH - N-CO, N-CO, N-Ø).

Anal. Calcd for $C_{37}H_{51}N_3O_5 \cdot C_4H_{10}O$: C, 71.16; H, 8.89; N, 6.07.
Found: C, 70.81; H, 8.60; N, 6.31.

4-Phenyl-1,2,4-triazoline-3,5-dione adduct (7) of 5,7,24-cholestatrien -3β-ol 3-acetate

To a stirred solution of the adduct 6 (1.50 g, 24.3 mmole) in dry benzene (320 ml) at 30 - 35° was added phosphorous pentoxide (about 5 g) in portions. After the dehydration was complete (about 1 - 1 1/2 hr), the supernatant solution was decanted onto cold sodium bicarbonate solution. The organic layer was separated, washed with cold water, brine and dried (Na_2SO_4). Removal of the solvent afforded the crude product which was purified by chomatography on silica gel (60 g). Elution with chloroform followed by elution with 1% acetone in chloroform gave 7 as a glass (1.18 g, 80%) : ir (nujol) 1760 and 1715 cm^{-1}; nmr ($CDCl_3$) δ 0.79 (s, 3H, 18-Me), 0.97 (s, 3H, 19-Me), 1.58 and 1.68 [two s, 6H, $=C(CH_3)_2$], 2.00 (s, 3H, CH_3CO), 3.21 (d of d, 1H, C-9-H), 5.07 (t, 1H, J = 7Hz, $-CH_2-CH=C<$), 5.5 (m, 1H, C-3-H), 6.16 and 6.40 (ABq, 2H, J = 8.5 Hz, C-6,7-H's) and 7.37 ppm (s, 5H, ArH); mass m/e 424 (M^+-AcOH) 364 (M^+-AcOH- N-CO, N-CO, N-Ø).

Anal. Calcd for $C_{37}H_{49}N_3O_4$: C, 74.09; H, 8.23; N, 7.01.
Found: C, 73.81; H, 8.29; N, 7.38.

5,7,24-Cholestatrien -3β-ol (5)

To a stirred suspension of lithium aluminum hydride (1.8 g) in dry tetrahydrofuran (200 ml) was added slowly a solution of compound 7 (1.0 g, 1.67 mmole) in tetrahydrofuran (100 ml). The mixture was heated to reflux under nitrogen for 1 1/4 hr. The mixture was cooled in an ice-bath and quenched with saturated aqueous sodium sulfate solution (about 150 ml). The organic layer was separated and the aqueous layer was extracted once with tetrahydrofuran (200 ml). The combined tetrahydrofuran extract was concentrated in vacuo and extracted with chloroform (2 x 200 ml). The chloroform solution was washed with brine, dried (Na_2SO_4) and evaporated to dryness. The crude product was purified by low temperature preparative thin layer chromatography on silica gel plates (2000 μ) at 5° in the dark and developed with 6.5% acetone in chloroform. The product was further recrystallized from methanol to give 5 (503 mg, 70%) : mp 104 - 107°; $[\alpha]_D$ = -122 ($CHCl_3$, C=0.77); uv (EtOH) λmax 263 (7,800), 271 (11,200), 282 (11,800), 293 nm (6,700); ir (nujol) νmax 3350 cm^{-1}; nmr ($CDCl_3$) δ 0.61 (s, 3H, 18-Me), 0.92 (s, 3H, 19-Me), 1.63 (d, 6H, J = 5 Hz, 26, 27-Me's), 3.6 (m, 1H, C-3-H), 5.09 (t, 1H, J = 6.5 Hz, C-24-H), 5.35 and 5.57 ppm (ABq, 2H, J = 5.5 Hz, C-6,7-H's); mass m/e 382 (M^+), 349 ($M^+ - H_2O - CH_3$), 323 ($M^+ - C_5H_9$).

Anal. calcd for $C_{27}H_{42}O$: C, 84.75; H, 11.07.
Found: C, 84.78; H, 10.89.

24-Dehydroprevitamin D_3 (8):

Compound 5 (330 mg) in deoxygenated ether (550 ml) was irradiated in a quartz photocell at 0 to 5° for 9 min using a 450 watt Hanovia medium pressure mercury vapor lamp while a small stream of nitrogen was bubbled through the solution. Thin layer chromatography on 5% silver nitrate impregnated silica gel (developed with 14% acetone in hexane) showed formation of a mixture containing 24-dehydrolumisterol$_3$ (R_f 0.12), starting material (R_f 0.37), 24-dehydrotachysterol$_3$ (R_f 0.50) and 24-dehydroprevitamin D_3 (R_f 0.57). The photo irradiated gross mixture was purified by low temperature preparative thin layer chromatography on silica gel plates (2000 μ) at 5° developed with 15-16% acetone in hexane for 3-4 times to give the purified 8 [nmr ($CDCl_3$) δ 0.71 (s, 3H, 18-Me), 0.95 (d, 3H, J = 5 Hz, 21-Me), 1.60 (s, 3H, 27-Me), 1.68 (s, 3H, 26-Me), 3.9 (m, 1H, C-3-H), 5.11 (t, 1H, J = 7 Hz, C-24-H), 5.52 (m, 1H, C-9-H), 5.67 and 5.99 ppm (ABq, 2H, J = 14 Hz, C-6, 7-H's)] free from contamination of 24-dehydrotachysterol$_3$ and the starting material 5 except the presence of ca. 5-10% 24-dehydrolumisterol$_3$.

24-Dehydrocholecalciferol (3):

The purified compound 8 (80 mg) was dissolved in deoxygenated absolute ethanol (5 ml) and heated to reflux for 2 hr under a nitrogen atmosphere. Thin layer chromatography on 5% silver nitrate impregnated silica gel developed with 20% acetone in hexane indicated the presence of 24-dehydrolumisterol$_3$ (R_f 0.18), the desired product 3 (R_f 0.46) and the starting material 8 (R_f 0.58) in the approximate proportions of 1:6:2. Purification of the mixture by low temperature preparative thin layer chromatography on silica gel plates (1000 μ) developed with 16% acetone in hexane for 3 times gave pure 3 as a glass (50 mg, 62%): uv (Et_2O) λmax 263 λmin 230 nm; ir (nujol) $\tilde{\nu}$max 3350 cm^{-1}; nmr ($CDCl_3$) δ 0.55 (s, 3H, 18-Me), 0.93 (d, 3H, J = 4.5 Hz, 21-Me), 1.59 (s, 3H, 27-Me), 1.67 (s, 3H, 26-Me), 3.9 (m, 1H, C-3-H), 4.80 (m, 1H, C-19-H), 5.02 (m, 2H, C-19-H and C-24-H), 5.97 and 6.23 ppm (ABq, 2H, J = 11.5 Hz, C-6, 7-H's); mass m/e 382 (M^+), 349 ($M-CH_3-H_2O$).

Acknowledgement

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