Studies on Vitamin D and Its Analogs. VI.[1,2] 3-Deoxy-*A*-homovitamin D_3, a Model Synthesis

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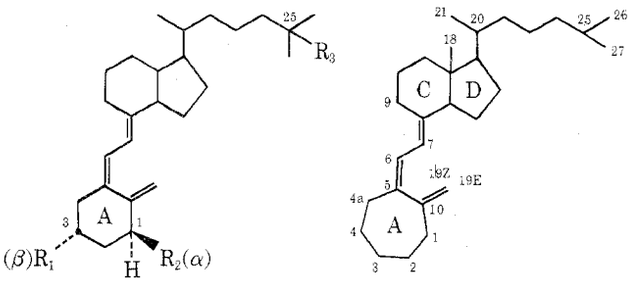
Vitamin D_3 (**1a**) undergoes an obligatory two-step metabolism to produce its biologically active form, 1α,25-dihydroxyvitamin D_3 (**1b**),[3] which acts biomechanistically like other classical steroid hormones.[4,5] The 1α-hydroxyl in **1b** appears to be critical for biological activity. Significant in this respect is the recent observation of the high biopotency of 3-deoxy-1α-hydroxyvitamin D_3 (**1c**), which we recently reported.[1b,6] In fact, **1c** was able to elicit a greater maximum in intestinal calcium transport than the natural metabolite **1b.** We rationalized this phenomenon in terms of a refined topological model for vitamin D_3 activity, which has, as a necessary requirement, an equatorial orientation of the 1α-hydroxyl group.[1a,6] In order to further probe this structure–function relationship, we have more recently directed our attention toward the synthesis of *A*-homo- and *A*-norvitamin D_3 analogs. This note describes the preparation of 3-deoxy-*A*-homovitamin D_3 (**2**).

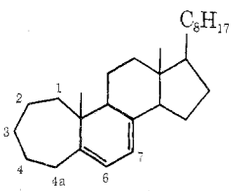
Because the synthesis of hydroxyl-substituted derivatives of **3** entails considerable effort, and since it was not obvious that **3** would isomerize by the well-known[7,8] (in the six-membered ring A series) two-step process to **2,** this model synthesis was carried out. This paper also demonstrates the conversion of the Δ^6-olefin **5** to the provitamin ($\Delta^{5,7}$-diene) **3.** Previously, only Δ^5-olefins had been used to obtain such provitamins.[9]

Diazomethane[10] was reacted with 5α-cholest-6-en-3-one[11] (**6**) in ether–methanol using the *ex situ* method[12] to afford the *A*-homo ketone mixture **7** in 58.5% yield. Nmr (300 MHz) analysis showed the mixture to contain a 60:40 ratio of **7a** to **7b.** Preparative high-pressure liquid chromatography resolved the mixture into pure **7a** and pure **7b.** Catalytic hydrogenation of **7a** afforded the known *A*-homo-5α-cholestan-3-one (**8a**)[13–15] and similar reduction of pure **7b** afforded the known 4-ketone (**8b**).[13] Catalytic hydrogenation of **7** followed by Wolff–Kishner reduction gave the known *A*-homo-5α-cholestane (**9**).[16,17] Similar Wolff–Kishner reduction of mixture **7** afforded 83% **5.**



1a, R_1 = OH; R_2 = R_3 = H
b, R_1 = R_2 = R_3 = OH
c, R_2 = OH; R_1 = R_3 = H

2



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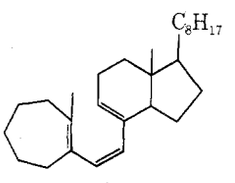

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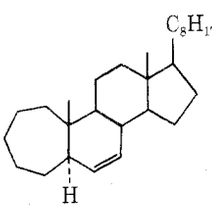

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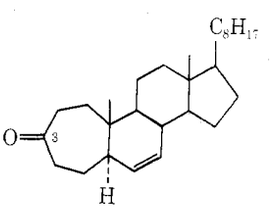
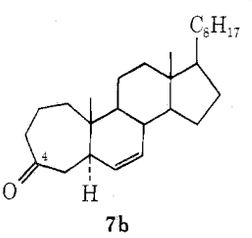


7a



7b

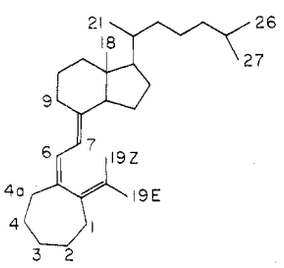


Figure 1. The 300-MHz nmr spectrum of 3-deoxy-*A*-homovitamin D_3 in $CDCl_3$ containing $CHCl_3$ and TMS as internal standards 2180 Hz apart.

The Δ^6-olefin **5** was treated successively with 1,3-dibromo-5,5-dimethylhydantoin and then trimethyl phosphite[9b] to afford a 39% yield of the provitamin **3** along with lesser amounts of *A*-homocholesta-4,6-diene (**10**). The structures of **3** and **10** were particularly evident from their nmr and uv spectra. Finally, it was gratifying to observe that after some experimentation, the *A*-homoprovitamin **3** could be isomerized to 3-deoxy-*A*-homovitamin D_3 (**2**). It is interesting that previtamins in the six-membered A-ring series are usually isolated when provitamins are irradiated under the conditions specified in the Experimental Section. In fact, it has been our usual practice to heat such previtamins for several hours at ~70° to effect isomerization to the vitamins. However, in the case of **3**, the initially formed previtamin was not observed even though a temperature of <30° was maintained. The 300-MHz nmr spectrum of **2** (Figure 1) is in accord with the assigned structure.[18] Studies now in progress are directed toward preparing *A*-homovitamins hydroxylated in the A ring.

Experimental Section

General. Infrared (ir) spectra were obtained with a Perkin Elmer 137 or 621 spectrophotometer and ultraviolet (uv) spectra with a Cary Model 14 spectrophotometer. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian spectrometer[2] with deuteriochloroform as solvent and tetramethylsilane (TMS, τ 10.00) and chloroform (τ 2.74) as the internal standards. Mass spectra were obtained with a Hitachi-Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by C. F. Geiger, Ontario, Calif. Melting points (mp, Thomas Hoover capillary melting point apparatus) are uncorrected. Low boiling petroleum ether (30–60°) is designated as lbpe.

***A*-Homo-5α-cholest-6-en-3- and -4-one (7).** The starting material **6** was prepared by previously described methods from cholesterol.[11] An ether solution of diazomethane, prepared from a mixture of ether (320 ml), diglyme (220 ml), aqueous sodium hydroxide (30%, 19 ml), and *N,N'*-dinitroso-*N,N'*-dimethylterphthalamide (70% suspension, 17.7 g, 0.12 mol),[10] was distilled over a 2.5-hr period into an ice cooled magnetically stirred solution of **6** (6.645 g, 0.0173 mol) in a mixture of ether (200 ml) and methanol (320 ml).[12] The solution was maintained at 0° for 3.5 hr and then at room temperature overnight. The colorless ether solution, upon concentration, afforded 7.2 g of crude, white solid. Column chromatography (120 g, Woelm neutral III alumina) was carried out by eluting with lbpe and ether–lbpe mixtures. Early fractions contained material (1.96 g) which was tentatively identified as an epoxide (ir, no C=O stretch; nmr), but this material was not investigated further. Later fractions afforded material (5.19 g) which upon crystallization from methanol (175 ml) gave the homo ketone mixture **7** (4.03 g, 58.5%) with mp 97–98° [ir (CCl_4) ν_{max} 1705 cm^{-1}; mass spectrum (80 eV) *m/e* 398 (parent ion)]. In other runs, the yield of pure ketone mixture varied between 45 and 60%. The mixture consisted of a 40:60 ratio of **7b/7a** as determined by examining the ratio of olefinic resonances and C_{19} angular methyl group resonances in the 300-MHz nmr spectrum.

Isolation of Pure 7a and 7b. The purified mixture **7** was subjected to preparative high-pressure liquid chromatography (hplc) (Waters Associates model ALC-202-401; 8 ft. × ⅜ in. porasil A preparative column; diisopropyl ether as solvent using a refractive index detector; 200 mg of **7** in 2 ml of diisopropyl ether injections) and two fractions were collected [faster eluting component (**7b**, minor) and more slowly eluting component (**7a**, major)]. Each fraction after concentration afforded residues which were individually recrystallized from methanol. The properties of pure **7a** and **7b**, each homogeneous to analytical hplc, were as follows.

7a (major): white needles; mp 91.0–92.0° (lit.[15] mp 91–92°); mass spectrum *m/e* 398 (parent ion); nmr (300 MHz) τ 4.51 and 4.79 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.18 (C_{19}–CH_3, s), and 9.31 (C_{18}–CH_3, s); **7b** (minor), white needles, mp 123.5–124.0° (lit.[15] mp 126–27°); mass spectrum *m/e* 398 (parent ion); nmr (300 MHz) τ 4.42 and 4.87 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.28 (C_{19}–CH_3, s), and 9.31 (C_{18}–CH_3, s).

Reduction of Pure 7a and 7b. The 3-one **7a** (40 mg) and 10% Pd/C (5 mg) in ethanol (10 ml) were subjected to hydrogenation. After work-up and recrystallization of the product, pure **8a** with mp 80.5–82.0° (lit.[13c] mp 83–85°) was obtained.

Identical reduction of pure 4-one **7b** afforded pure **8b** with mp 94.0–95.5° (lit.[13c,14] mp 96–97°).

Conversion of Mixture 7 to *A*-Homo-5α-cholestane (9). The ketone mixture **7** (0.500 g, 0.0125 mol) and 10% palladium on charcoal (100 mg) in absolute ethanol (125 ml) absorbed 40 ml of hydrogen (0.016 mol, 24° (733 mm)) over a 4-hr period. The catalyst was removed by filtration and thoroughly washed with ether. The filtrate upon evaporation afforded 470 mg of crude white solid which was identical with a mixture of *A*-homo-5α-cholestan-3-one and -4-one (**8**)[17] prepared by diazomethane ring expansion of 5α-cholestan-3-one.

The entire crude white solid was dissolved in diethylene glycol (30 ml) in a 100-ml three-necked round-bottom flask fitted with a condenser, thermometer, and a nitrogen inlet. Hydrazine (5 ml) and potassium hydroxide (0.85 g) were added and the mixture was refluxed at 135° for 1 hr. The condenser was replaced with a distillation head and the reaction temperature was allowed to rise to 235°. After 3.5 hr, the mixture was cooled and water (50 ml) was added. The mixture was extracted with ether (2 × 75 ml) and then the ether solution was washed with water (2 × 50 ml), dried (sodium sulfate), and then concentrated to a yellow oily residue. Chromatography (15 g, Woelm neutral I) with lbpe afforded 230 mg of a white solid. Crystallization from methanol (50 ml) afforded pure *A*-homo-5α-cholestane (**9**) with mp 87.5–89.0° (lit.[16] mp 92–94°): nmr (300 MHz) τ 9.11 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.26 (C_{19}–CH_3, s), and 9.36 (C_{18}–CH_3, s).

***A*-Homo-5α-cholest-6-ene (5).** The Wolff–Kishner reduction of ketone mixture **7** was carried out in the same manner as described in the immediately preceding section[16] (**7**, 2.0 g, 0.0050 mol; diethylene glycol, 120 ml; KOH, 3.6 g; hydrazine 20 ml). After work-up and chromatography (50 g of Woelm neutral I with lbpe), the crude product (2.0 g) was crystallized (absolute ethanol) to afford 1.60 g (83%) of pure **5**: mp, 96.0–97.5°; nmr (300 MHz) τ 4.53 and 4.79 ($H_{6,7}$, AB q, J_{AB} ~ 10.0 Hz), 9.10 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), 9.26 (C_{19}–CH_3, s), and 9.32 (C_{18}–CH_3, s).

Several recrystallizations afforded the sample submitted for analysis.

Anal. Calcd for $C_{28}H_{48}$: C, 87.42; H, 12.58. Found: C, 87.15; H, 12.88.

***A*-Homo-5α-cholesta-5,7-diene (3) and *A*-Homo-5α-cholesta-4,6-diene (10).** To a refluxing solution of **5** (1.935 g, 0.00503 mol) in 1:1 benzene–lbpe (80 ml) was added powdered 1,3-dibromo-5,5-dimethylhydantoin (1.0 g, 0.0035 mol) at once. The refluxing solution turned pale yellow immediately and then lemon yellow within 5 min. After a total of 15 min at reflux, the mixture was ice cooled and then filtered to remove the precipitated 5,5-dimethylhydantoin (ice cold lbpe washings). The solution was concentrated to a yellow oily residue under vacuum at below room temperature.

The residue in xylene (20 ml) was added dropwise under nitrogen to a magnetically stirred, refluxing solution of trimethylphosphite (3.0 ml) in xylene (60 ml). After 1.5 hr of reflux, the mixture was cooled and then concentrated to dryness under high vacuum. The resulting yellowish brown semisolid was chromatographed over 100 g of 10% silver nitrate impregnated Woelm neutral alumina. The elution was carried out successively with lbpe and ether–lbpe mixtures. Earlier fractions afforded 1.079 g of crude $\Delta^{5,7}$-diene **3** which upon crystallization afforded 750 mg (39%) of material with mp 75.5–77.0°. Later fractions afforded 435 mg of a mixture of **10** (mainly) and starting material **5**. Crystallization of the mixture afforded pure **10**.

The $\Delta^{5,7}$-diene **3** exhibited the following: nmr (300 MHz) τ 4.46 and 4.63 ($H_{6,7}$, AB q, J_{AB} ~ 6.0 Hz; B further split into t, J ~ 2.8 Hz), 9.06 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.10 (C_{19}–CH_3, s), 9.13 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), and 9.40 (C_{18}–CH_3, s); uv (ether) λ_{max} (ϵ) 255 sh (5660), 266 sh (9870), 274 (13,800), 285 (14,100), 297 (7790) nm. Several recrystallizations afforded the sample submitted for analysis.

Anal. Calcd for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 88.12; H, 12.27.

The $\Delta^{4,6}$-diene **10** exhibited the following: nmr (300 MHz) τ 4.13 (H_7, dd, J ~ 10.0, 2.5 Hz), 4.48 (H_{4a}, t, J ~ 6.4 Hz), 4.53 (H_6, d, J ~ 10.0 Hz), 9.03 (C_{19}–CH_3, s), 9.09 (C_{21}–CH_3, d, J ~ 6.5 Hz), 9.13 ($C_{26,27}$–$2CH_3$, d, J ~ 6.5 Hz), and 9.29 (C_{18}–CH_3, s); uv (ether) λ_{max} 238 nm.

Repeated recrystallization of this material afforded the sample submitted for analysis, mp 88.5–89.5°.

Anal. Calcd for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 87.49; H, 12.45.

3-Deoxy-*A*-homovitamin D_3 (2). The photochemical apparatus consisted of a Hanovia quartz immersion well (Cat. No. 19434) fitted with a 125-ml reaction vessel (equipped with a condenser and nitrogen inlet) and a Hanovia 200-W medium-pressure mercury arc (Cat. No. 654A-36) with a No. 9700 Corex filter sleeve. The lamp was prewarmed for 15 min before exposing the ice cooled reaction solution to irradiation for 3.0 min. The solution was purged thoroughly with nitrogen prior to and during the irradiation. Four irradiation mixtures (125 mg of **3**/100 ml of ether each; 500 mg total) were pooled and concentrated at <30° under vacuum to afford an oily semicrystalline residue. Nmr and uv analysis indicated the residue to contain mainly a mixture of **3** and **2.** Chromatographic separation (140 g, 10% silver nitrate impregnated Woelm neutral alumina prepared with lbpe, 28-mm diameter column) was carried out using lbpe and lbpe–ether combinations.

Early fractions afforded starting material **3** (256 mg, 51%) while later fractions proved to be the homovitamin D **2** (90 mg, 18%; 37% based on recovered **3**). The semicrystalline homovitamin is exceedingly air-sensitive. Prior to measuring any of its physical properties, it was purified by rechromatography (with lbpe on a 15-g Woelm neutral I column) and the single fraction obtained was evacuated to dryness. The nmr spectrum (300 MHz) shown in Figure 1 revealed the following: τ 3.74 and 3.97 ($H_{6,7}$, AB q, $J_{AB} \sim$ 11.0 Hz), 4.93 H_{19Z}, br with a fine structure, $W \sim 6$ Hz), 5.12 (H_{19E}, d, $J \sim 2.2$ Hz; $W \sim 5$ Hz), 7.18 ($H_{9\beta}$, d, $J \sim 12$ Hz), 7.67 ($H_{1\alpha,1\beta,4a\alpha,4a\beta}$, br s, $W \sim 13$ Hz), 9.08 (C_{21}–CH_3, d, $J \sim 6.5$ Hz), 9.14 ($C_{26,27}$–$2CH_3$, d, $J \sim 6.5$ Hz), and 9.46 (C_{18}–CH_3, s); uv (95% ethanol) ϵ_{max} (ϵ) 244 sh (14,000), 252 (16,300), 261 (16,400), 275 br sh (15,100) and λ_{min} 230 (10,700) nm; mass spectrum (80 eV) *m/e* 382 (parent ion).

Registry No.—**2,** 52920-82-8; **3,** 52920-83-9; **5,** 52920-84-0; **6,** 52949-49-2; **7a,** 35569-96-1; **7b,** 35569-95-0; **9,** 24366-12-9; **10,** 52920-85-1; diazomethane, 334-88-3; 1,3-dibromo-5,5-dimethylhydantoin, 77-48-5.

Reference and Notes

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(2) We are grateful to Professor David Kearns for the 300-MHz nmr spectra. This research was generously supported by grants from the U. S. Public Health Service (AM-16595) and the Intramural Research Fund, University of California, Riverside. We especially acknowledge Professors A. W. Norman and R. M. Wing for their informative comments during the course of this study.

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Oxidation of 4-Phenylurazole with Activated Isocyanates and Dimethyl Sulfoxide

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During an investigation of the chemical reactivity of 4-phenyl-1,2,4-triazoline-3,5-dione (**3**), we observed that reaction mixtures in dry (molecular sieves) dimethyl sulfoxide (DMSO) containing 4-phenylurazole (**1**) turned bright red and emitted an unpleasant odor upon addition of trichloroacetyl isocyanate[11] (**2a**). DMSO has been used in a number[1] of oxidizing systems in recent years, *e.g.*, DMSO–dicyclohexyl carbodiimide–H_3PO_4,[2] DMSO–acetic anhydride[3a] (and similar systems **3b**), DMSO–ketenimine,[4] and DMSO–SO_3–pyridine.[5] The rapidity with which the reaction occurred, the intensity of the characteristic red color of **3** which formed, and the increased usage of **3** as a dieneophile and as a chemical reagent in the current literature prompted us to investigate the utility of this pathway as an easy and rapid route to **3**.[6–10]

Purified acetonitrile was found to be the ideal solvent for a spectrophotometric assay for **3** (λ_{max}^{525}, ϵ 157). Under controlled conditions, the products observed when **2a** was reacted with **1** in DMSO were carbon dioxide (as barium carbonate), dimethyl sulfide (trapped at −80° and characterized as trimethyl sulfonium iodide), trichloroacetamide[12] (essentially insoluble in cold $CHCl_3$), and **3** (isolated by sublimation and characterized by spectroscopic comparisons with an authentic sample).[9] The average yield, determined spectrophotometrically, was 98% with **2a.** Difficulty was encountered in isolating pure **3** from this reaction (~20% yield by sublimation) but this is the only respect in which this new reagent suffers in comparison with the other methods. The chemical reactivity of **3** was shown to be unaffected by the system by isolation of its adduct with cyclobutadiene. The major advantage of this approach lies in the rapidity with which **3** may be generated *in situ.* At room temperature, the reaction is over almost instantaneously. Since the isocyanates used and **1** are indefinitely stable, this provides an instantaneous source of **3** in a highly polar solvent (DMSO). N_2O_4 and *t*-BuOCl are relatively unpleasant materials to work with while the isocyanates used herein can be readily transferred in measured amounts with a hypodermic syringe.

Only isocyanates activated by strongly electron-withdrawing substituents were effective. The reaction with *p*-toluenesulfonyl isocyanate (**2b**) was essentially indistinguishable from that with **2a,** benzoyl isocyanate (**2c**) gave 88% of **3,** while phenyl and *n*-butyl isocyanates gave less than 10% conversion in very slow reactions which stopped