mL), water (2 × 30 mL), and then acetone. The precipitate was dried overnight and heated with a solution of 4 g of EDTA in 120 mL of water on a steam bath for 30 min. The mixture was left overnight. The tan colored solid was filtered off and washed with water to give 3.2 g (89%) of **2**: mp 218–222 °C; ^{1}H NMR (TFA) δ 3.45–3.85 (m, 2 H), 4.50–5.05 (m, 1 H), 7.20–8.20 (br d, 9 H); $[\alpha]^{25}_{546}$ −14.95° (*c* 2.0, HOAc). Anal. Calcd for $C_{16}H_{15}N_5O_3 \cdot H_2O$: C, 55.97; H, 4.96; N, 20.41. Found: C, 55.62; H, 5.05: N, 20.73.

Similarly L-[3',5'-$^{13}C_2$]tyrosine (1.5 g) gave 2.2 g (82%) of the corresponding tetrazolyl ether: ^{1}H NMR (TFA) δ 3.40–3.75 (m, 2 H), 4.50–5.00 (m, 1 H), 5.88–6.25 (m, 1 H), 7.30–8.00 (m, 7 H), 8.83–9.20 (m, 1 H); ^{13}C NMR (TFA–D_2O) 102.47.

L-Phenylalanine (3). **2** (1.0 g) was dissolved in absolute ethanol (70 mL) and acetic acid (40 mL) by warming on a steam bath. The solution was cooled to room temperature, and cyclohexene (30 mL) was added followed by 5% Pd–C (2.0 g). The mixture was refluxed for 2.0 h at 100 °C. It was then evaporated to dryness, and the residue was stirred with water (3 × 100 mL) and filtered. The filtrate was evaporated to dryness, and the residue was crystallized from water–ethanol to yield 0.35 g (69%) of L-phenylalanine, $[\alpha]^{25}_{546}$ −39.2° (*c* 2.0, H_2O) [lit.[5] $[\alpha]^{25}_D$ −34.5° (*c* 2, H_2O)]. TLC behavior in solvent systems A, B, and C was identical with that of authentic L-phenylalanine.

Similarly the tetrazolyl ether of L-[3',5'-$^{13}C_2$]tyrosine (1 g) furnished 0.34 g (68%) of L-[3',5'-$^{13}C_2$]phenylalanine: ^{1}H NMR (D_2O) δ 3.35–3.60 (m, 2 H), 4.20–4.60 (m, 1 H), 5.00 (H_2O), 6.10–6.60 (m, 1 H), 7.45–7.80 (br d, 3 H), 8.68–9.24 (m, 1 H); ^{13}C NMR (D_2O) 129.95.

***N*-(*tert*-Butyloxycarbonyl)-L-[3',5'-$^{13}C_2$]phenylalanine (6).** The filtrate from the crystallization of labeled phenylalanine was evaporated to dryness, and the residue (0.1 g) was stirred with S-Boc-4,6-dimethyl-2-mercaptopyrimidine[7] (0.2 g), dioxane (0.5 mL), water (0.5 mL), and triethylamine (0.25 mL) overnight. The solution was diluted with water (5 mL) and extracted with ethyl acetate (3 × 20 mL). The aqueous solution was cooled to 0 °C and the pH was brought to 2.5 with 4% hydrochloric acid cooled to 0 °C. The mixture was saturated with sodium chloride and extracted with ethyl acetate (3 × 30 mL). The ethyl acetate solution was washed with 4% ice-cold hydrochloric acid (3 × 10 mL) and water (3 × 10 mL) and dried over anhydrous sodium sulfate, and the solvent was removed. The residue was crystallized from ether–petroleum ether to give 0.035 g of **6**: mp 83–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 2.90–3.25 (m, 2 H), 4.20–4.80 (m, 1 H), 4.80–5.45 (m, 1 H), 5.65–6.20 (m, 1 H), 7.00–7.50 (br d, 3 H), 8.32–8.81 (m, 1 H), 11.49 (br s, 1 H).

L-Tyrosine Benzyl Ester (4). A mixture of L-tyrosine (1.4 g), concentrated hydrochloric acid (4 mL), and benzyl alcohol (40 mL) was heated at 100 °C for 15 min to give a clear solution. Benzene (20 mL) was added, the solution was heated at 100–105 °C, and water was removed azeotropically for 2.5 h. More concentrated hydrochloric acid (1 mL) was added, and heating was continued for another 30 min. The mixture was cooled and diluted with ether (50 mL). The mixture was extracted with dilute hydrochloric acid (5 × 20 mL) and water (2 × 20 mL). The combined aqueous solution was washed with ether, and the pH was brought to 8 with dilute NH_4OH. The mixture was left overnight and the solid was filtered, washed with water, and dried. The white solid was stirred with acetone (100 mL) and filtered to give 50 mg of tyrosine. The filtrate was evaporated to give a gum which solidified to yield 1.6 g (80%) of **4**: mp 110–114 °C (lit.[6] mp 120 °C); ^{1}H NMR ($CDCl_3$–Me_2SO-d_6) δ 2.80–3.00 (m, 2 H), 3.6–4.2 (m, 4 H), 5.16 (s, 2 H), 6.75 (d, 2 H), 6.95 (d, 2 H), 7.35 (s, 5 H).

1-Phenyltetrazolyl Ether of L-Tyrosine Benzyl Ester (5). A mixture of 0.75 g of L-tyrosine benzyl ester (**4**), 1-phenyl-5-chlorotetrazole (0.5 g), and anhydrous K_2CO_3 (2.5 g) in acetone (80 mL) was refluxed overnight. The mixture was evaporated to dryness. The residue was treated with water and filtered to give 1.05 g (92%) of **5**, mp 90–95 °C. An analytical sample was obtained by recrystallization from ethyl acetate and hexane: mp 92–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.70–1.90 (m, 2 H), 2.95–3.15 (m, 2 H), 3.60–3.90 (m, 1 H), 5.10 (s, 2 H), 7.30–7.80 (m, 14 H). Anal. Calcd for $C_{23}H_{21}N_5O_3 \cdot {}^1/_2H_2O$: C, 65.09; H, 5.18; N, 16.51. Found: C, 65.21; H, 5.36; N, 16.71.

L-Phenylalanine (3). A mixture of 1 g of **5** and 5% Pd–C (2 g) in ethanol (15 mL) and cyclohexene (10 mL) was refluxed for 2 h at 100 °C. L-Phenylalanine, 0.24 g (62%), $[\alpha]^{25}_{546}$ −37.0° (*c* 2, H_2O), was isolated as before. TLC behavior in solvent systems A, B, and C was identical with that of authentic L-phenylalanine.

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Registry No. 1, 60-18-4; 1 (3',5'-$^{13}C_2$), 70479-98-0; 2, 73198-07-9; 2 (3',5'-$^{13}C_2$), 73198-08-0; 3, 63-91-2; 3 (3',5'-$^{13}C_2$), 73198-09-1; 4, 42406-77-9; 5, 73198-10-4; 6, 73198-11-5; 1-phenyl-5-chlorotetrazole, 14210-25-4; S-Boc-4,6-dimethyl-2-mercaptopyrimidine, 41840-28-2.

Effect of C-21 Substituents on the Elimination of a 17α-Acyloxy Group from 17α-(Acyloxy)-20-oxo Steriods

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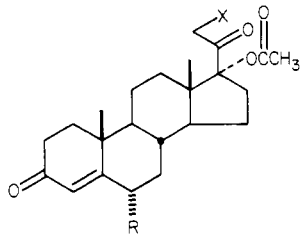
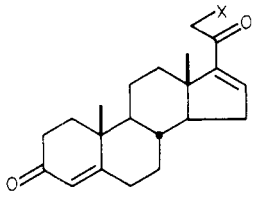
In 1970, Salce, Hazen, and Schoenewaldt[1] reported that heating 17α-acyloxy derivatives of 20-oxo steroids at 105 °C in dimethylformamide containing potassium acetate results in elimination of the acyloxy function to form 16-dehydro-20-oxo steroids. We noted that while the above procedure was described as a general method, all of the compounds cited as starting materials actually were 17α,21-bis(acyloxy)-20-oxo steroids. We report here a study of the effect of the C-21 substituents on the course of the above reaction.

When submitted to reaction conditions similar to those described by Salce et al.[1] 17α,21-diacetoxy-4-pregnene-3,20-dione (**1**) was converted to 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**) in 62% yield. In contrast, 17α-acetoxy-6α-methyl-4-pregnene-3,20-dione (**3**) was recovered unchanged under similar conditions. If the latter compound was heated overnight in refluxing dimethylformamide containing potassium acetate, it decomposed to a complex mixture which did not contain an appreciable amount of the expected product.



1, R = H; X = OC(O)CH
3, R = CH_3; X = H
4, R = H; X = OH
5, R = H; X = Cl
6, R = H; X = OTHP



2, X = $OC(O)CH_3$

When 17α,21-dihydroxy-4-pregnene-3,20-dione 17-acetate (**4**) was heated under conditions similar to those of Salce et al.[1] it reacted by a transacylation to afford the

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21-acetate in 51% yield. Under similar conditions, 17α-acetoxy-21-chloro-4-pregnene-3,20-dione gave mainly recovered starting material and the 17α-hydroxy-21-acetoxy derivative with lesser amounts of four other steroidal products, none of which appeared to be the product of elimination.

The 21-tetrahydropyranyl ether of 17α-acetoxy-21-hydroxy-4-pregnene-3,20-dione (**6**) reacted to give, in 75% yield, 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**). We find this particularly suprising both because of the failure of **4** to undergo elimination and because Salce et al.[1] reported that 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione 17-caproate 21-acetate reacts by simple elimination of caproic acid.

The above experiments establish that the elimination reaction is not general but rather that it occurs only when selected functional groups are present at C-21. The mechanism by which the C-21 acyloxy and tetrahydropyranyloxy groups facilitate the elimination of 17α-acyloxy groups remains to be established.

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer 297 spectrometer. NMR spectra were determined on a Varian T-60 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc.

The known[4] 17,21-dihydroxy-4-pregnene-3,20-dione 17-acetate (**4**) was prepared from cortexolone essentially according to the procedure of Gardi, Vitali, and Ercoli,[2] but substituting triethyl orthoacetate for trimethyl orthoacetate. Acetylation of **4** with acetic anhydride–pyridine gave the known[5] diacetate **1**. 17α-Acetoxy-21-chloro-4-pregnene-3,20-dione (**5**) was synthesized essentially according to the procedure of Bergstrom, Sollman, Nicholson, and Dodson.[3] 17α-Acetoxy-6α-methyl-4-pregnene-3,20-dione (**3**) was purchased from the Sigma Chemical Co. All of the above compounds were pure by TLC, had melting points in agreement with literature values, and showed the expected IR and NMR spectra.

Synthesis of 17α-Acetoxy-21-(tetrahydropyranyloxy)-4-pregnene-3,20-dione (6). To 200 mg of **4** in 3 mL of freshly distilled dihydropyran was added 1 crystal of *p*-toluenesulfonic acid monohydrate. The solution was stirred for 3–4 h and then partitioned between ethyl ether and water. The ether layer was dried and distilled to leave a residue of 370 mg of an oil which crystallized from acetone–hexanes to afford **6**: yield 121 mg (50%); mp 147–148 °C; NMR ($CDCl_3$) δ 0.72 (s, C-18 H's), 1.20 (s, C-19 H's), 2.09 (s, $OC(O)CH_3$), 4.33 (m, C-21 H's), 4.64 (m, C-1′ H), 5.75 (m C-4 H). Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 71.15; H, 8.52.

Elimination Reaction on 17,21-Diacetoxy-4-pregnene-3,20-dione (1). To a solution of 100 mg of **1** (0.232 mmol) in 4 mL of DMF was added 49 mg of potassium acetate (0.499 mmol). The mixture was stirred at 105 °C, under nitrogen, for 6 h. The mixture then was cooled and poured into ice–water. The crystals which precipitated were collected by filtration, washed with water, and dried to afford 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**): yield 53 mg (62%); mp 153–154 °C (lit.[6] mp 153–154 °C); NMR ($CDCl_3$) δ 0.96 (s, C-18 H's), 1.23 (s, C-19 H's), 2.20 (s, $OC(O)CH_3$), 4.96 (dd, C-21 H's), 5.73 (m, C-4 H), 6.73 (m, C-16 H).

Attempted Elimination Reaction on 17α-Acetoxy-6α-methyl-4-pregnene-3,20-dione (3). A. A solution of 100 mg of **3** was reacted under the conditions described for **1**. After workup, starting material was recovered in a yield of 70%.

B. The reaction was repeated on a fresh batch of 100 mg of **1** with heating being maintained overnight. The reaction product was an oil which gave an unresolvable streak on TLC under a variety of conditions.

Attempted Elimination Reaction on 17α,21-Dihydroxy-4-pregnene-3,20-dione 17-Acetate (4). A mixture of 100 mg of **4** (0.257 mmol) and 55 mg of potassium acetate (0.560 mmol) in 4 mL of DMF was stirred, under nitrogen, at 105 °C for 6 h. The mixture was cooled and then partitioned between ether and water. From the organic phase was isolated 17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate: yield 51 mg (51%); mp 235–240 °C (lit.[7] mp 235–238 °C).

Attempted Elimination Reaction on 17α-Acetoxy-21-chloro-4-pregnene-3,20-dione (5). A mixture of 115 mg of **5** (0.283 mmol) and 61 mg of potassium acetate (0.611 mmol) in 2.5 mL of DMF was stirred at 105 °C for 5 h, under nitrogen. The mixture was cooled and partitioned between $CHCl_3$ and H_2O. From the organic layer was obtained 80 mg of a dark oil which showed six main spots on TLC. By the use of preparative TLC, small quantities of pure starting material, **5**, and of 17,21-dihydroxy-4-pregnene-3,20-dione 21-acetate could be isolated. The remaining material was not definitively characterized but, as judged by TLC and NMR properties, it did not appear to contain any of the desired product of elimination.

Elimination Reaction on 17α-Acetoxy-21-(tetrahydropyranyloxy)-4-pregnene-3,20-dione (6). A mixture of 80 mg of **6** (0.169 mmol) and 36 mg of potassium acetate (0.367 mmol) in 2 mL of DMF was stirred, under nitrogen, at 105 °C for 5 h. The mixture was cooled and partitioned between CH_2Cl_2 and H_2O. The residue from the organic phase crystallized from acetone–hexanes to afford 21-acetoxy-4,16-pregnadiene-3,20-dione (**2**) in a yield of 47 mg (75%; identical in melting point, NMR, and TLC behavior with that formed from **1**).

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Registry No. **1**, 1807-15-4; **2**, 37-413-94-8; **3**, 74-58-9; **4**, 19357-45-0; **5**, 57273-80-0; **6**, 73275-17-9; 17α,21-dihydroxy-4-pregnene-3,20-dione 21-acetate, 640-87-9.

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Synthesis of a 14α-Methyl Vitamin D Precursor

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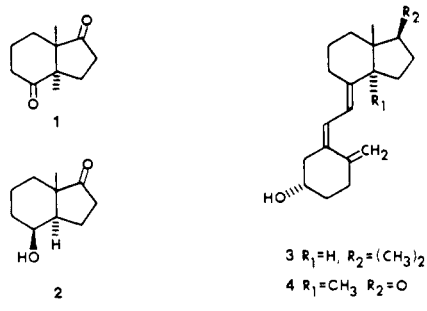
The potential usefulness of *trans*-1,6-dimethylbicyclo[4.3.0]nonan-2,7-dione (**1**) as an intermediate in terpene



synthesis has been noted.[1,2] Since this diketone resembles the bicyclic intermediate **2** used by Inhoffen[3] in a landmark

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