Unusual Air Oxidations of 6-Fluoroandrost-5-en-3-ones and Their Hydrazone Derivatives[1]

Sharada S. Labadie

Syntex Research, Palo Alto, California 94304

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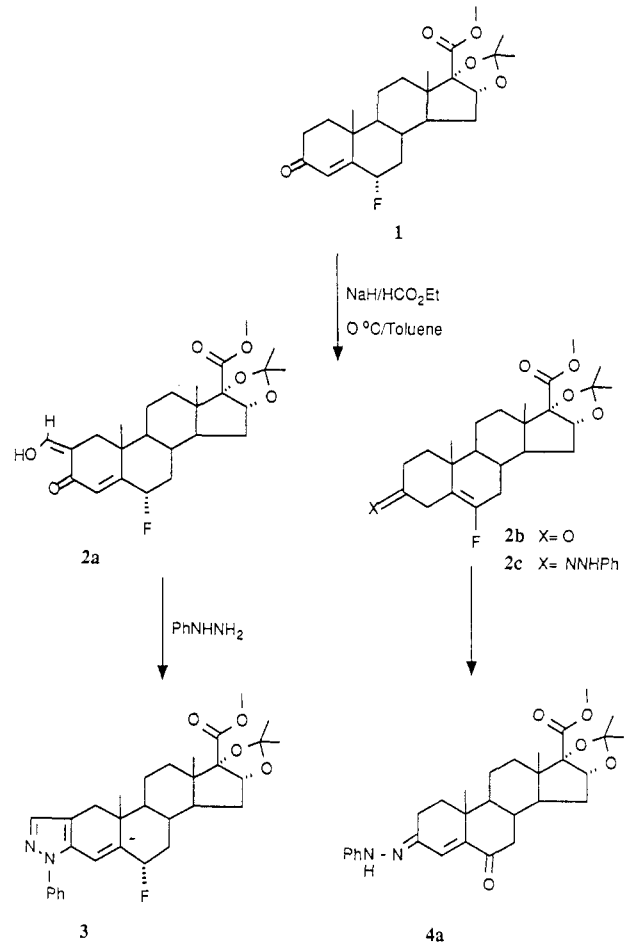
In the presence of phenylhydrazine under an atmosphere of air 6-fluoroandrost-5-en-3-one (**2b**) underwent oxidative defluorination to give 6-keto 3-hydrazone **4a**. A mechanistically related oxidation of **2b** to 4-ene-3,6-dione **4b** was observed to occur in toluene containing sodium methoxide and also in chloroform.

A-ring fused [3,2-*c*]pyrazoles have been shown to be potent agonists of the corticosteroid receptor.[2] In order to expand the structure–activity relationship in this series of steroids, we required several 6α-fluoro-substituted [3,2-*c*]pyrazoles, since 6α-fluoro substitution of corticosteroids is associated with enhanced antiinflammatory activity.[3] Typically, steroidal pyrazoles have been prepared by the hydroxymethylenation of the steroid using ethyl formate in the presence of sodium hydride,[4] followed by the condensation of the resulting adduct with substituted hydrazines.[4,5] However, in the present study involving 6-fluoro-substituted steroid **1**, the hydroxymethylenation was problematic and gave a mixture of two components. Subsequent treatment of this mixture, without purification, with phenylhydrazine in methanol provided the desired pyrazole **3** and an unexpected oxidation product characterized as the 6-keto 3-hydrazone **4a** by its elemental analysis and spectral data. The ^{1}H NMR spectrum of this compound showed a sharp singlet at δ 7.08 lacking the long-range coupling to the 6β-hydrogen observed in the starting material **1**. The ^{13}C NMR spectrum of **4a** displayed carbonyl resonances at 198 and 172 ppm, corresponding to a ketone and an ester, respectively, and an additional signal at 143 ppm, possibly corresponding to the —C=N group of the hydrazone. The structure was further confirmed by its mass spectrum which displayed a molecular ion at m/z 506 ($C_{30}H_{38}N_2O_5$). Closer examination of the initial product of the hydroxymethylenation reaction showed this to be a mixture of the desired product **2a** and the deconjugated ketone **2b**, the latter apparently being the precursor for the 6-keto 3-hydrazone **4a**. Since, to our knowledge, this type of transformation is not reported in the literature, we investigated this interesting reaction further and wish to describe studies on the oxidation of the deconjugated ketone **2b**.

The hydroxymethylenation reaction of **1** with an excess of sodium hydride (50% dispersion) and ethyl formate in toluene under a nitrogen atmosphere at 0 °C gave a 50:50 mixture of **2a** and **2b** after chromatographic purification. The deconjugated ketone **2b** could also be obtained in approximately 50% yield by treating **1** with 5–10 equiv of freshly prepared sodium methoxide in toluene under scrupulously deoxygenated conditions. The condensation of **2b** with phenylhydrazine in methanol under an atmosphere of air gave **4a** cleanly in 70% yield [Scheme I]. Since aerobic oxidation was suspected in the transformation, the deconjugated ketone **2b** was treated with phenylhydrazine in deoxygenated methanol. In contrast to

Scheme I



the result described above, a new component was formed which was unstable to aerobic exposure. This intermediate, however, was isolated by rapid flash chromatography along with **4a** and found to be the 3-hydrazone **2c**, still retaining the deconjugation, as evidenced by the ^{1}H NMR spectrum which showed resonances at δ 3.10 and 2.60, corresponding to methylene protons of the 4-position. Upon allowing this intermediate to stand in $CDCl_3$ in an NMR tube, another component with a sharp singlet at δ 7.37 (different to the δ 7.08 of **4a**) formed, and the signals at δ 3.10 and 2.60 disappeared. This intermediate transformed itself to the previously observed 6-keto 3-hydrazone **4a**, indicating that the hydrazone **2c** undergoes oxidative transformation via an unstable intermediate.

The ketone **1** was treated with phenylhydrazine in methanol under aerobic conditions to rule out the possibility that **1** was an intermediate in the oxidative transformation. A major product different from **4a** was formed and identified as the diazo compound **5**. This structure was substantiated by its spectral data and elemental

(1) Contribution no. 750 from the Institute of Organic Chemistry.
(2) Hirschmann, R.; Steinberg, N. G.; Buchshacher, P.; Fried, J. H.; Kent, G. J.; Tishler, M.; Steelman, S. L. *J. Am. Chem. Soc.* **1963**, *85*, 120.
(3) Wolff, M. E. In *Burger's Medicinal Chemistry*, 4th ed, Part III; Wolff, M. E., Ed.; Wiley-Interscience: New York, 1981; pp 1305–1306.
(4) Clinton, R. O.; Clarke, R. L.; Stanner, F. W.; Manson, A. J.; Jennings, K. F.; Phillips, D. K. *J. Org. Chem.* **1962**, *27*, 2800.
(5) Fried, J. H.; Buchshacher, P.; Mrozik, H. *Steroids* **1963**, *2*, 399.

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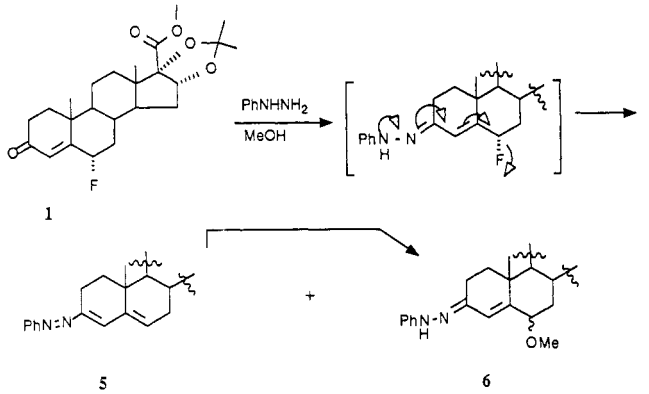
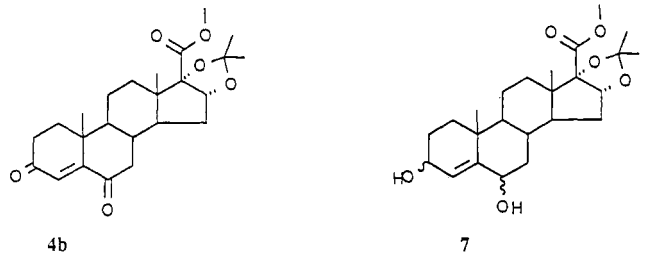
Scheme II



analysis. The presence of a broad singlet at δ 7.06 (C4-H) and a broad triplet at 5.97 (C6-H) is indicative of a 3,5-diene system, and the product can be explained by analogy to the well-precedented Wharton rearrangement.[6] The minor product of this reaction was characterized as the 6-methoxy 3-hydrazone, **6**, apparently formed by further addition of methanol to **5** (Scheme II).[7] None of **4a** was present as evidenced by TLC, thus indicating that **1** is not an intermediate in the oxidative transformation of **2b**.

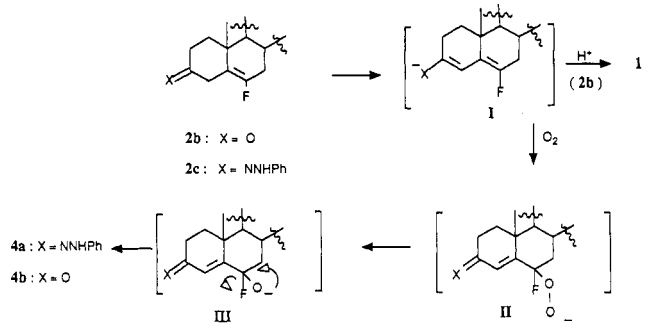
The 6-fluoro deconjugated ketones of the type **2b** have been cited in the literature[8] as intermediates in the epimerization of 6β-fluoro compounds to 6α-fluoro analogues. In these cases, the treatment of the deconjugated ketone with sodium methoxide in methanol and then neutralization with 90% acetic acid provides 6α-fluoro derivatives. The ketone **2b** was treated with 5 equivalents of sodium methoxide in methanol under aerobic conditions for several hours and the solvent was removed on a rotary evaporator. The residue was found to be a 3:1 mixture of **1** and **4b** as determined by ^{1}H NMR analysis. The diketone **4b** was the sole product when toluene was used as the solvent. Again, when the reaction in toluene was performed in the absence of air, the starting material **2b** remained unchanged. The presence of the two keto groups in **4b** was further confirmed by the reduction of **4b** to the diol **7** with sodium borohydride. Apparently, this oxidative trans-



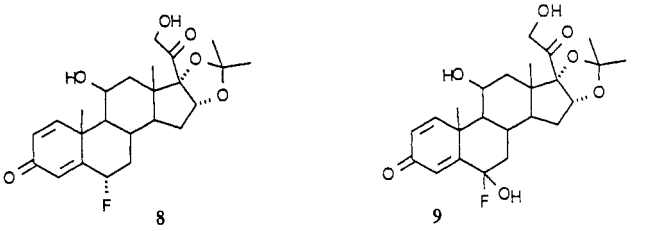
formation occurs through the base-catalyzed enolization and subsequent trapping either by a proton or molecular oxygen in a protic solvent or solely by molecular oxygen in the absence of a proton source.

The in vitro oxidative defluorination of flunisolide (8) and related 6α-fluoro steroids to 6-keto derivatives by the mouse liver microsomes[9] and by fungus *Rhizopus arrhius*

Scheme III



ATCC is well-documented.[10] The transformation is postulated to proceed via halohydrin intermediate **9**, and



a similar intermediate can be envisioned in the air oxidation of **2b**. The formation of this intermediate can be likened to the well-precedented[11] base-catalyzed air oxidation of α-cyano esters to α-keto esters. The air oxidation of α-cyano esters is known to proceed via peroxy intermediates followed by disproportion to the α-keto esters. A similar reaction pathway can be invoked for the air oxidation of **2b** and **2c**. The enolate, **I** (Scheme III), formed by sodium methoxide or phenylhydrazine, is trapped by a proton in methanol to give **1**. In the absence of methanol, the presumption is that oxygen is trapped to give a peroxy intermediate,[12] **II**, which disproportionates to the intermediate **III** as in the oxidation of α-cyano esters. The intermediate **III** subsequently eliminates fluoride ion to give either diketone **4b** or keto hydrazone **4a**. However, in case of the reaction of **2b** with phenylhydrazine in methanol, none of the 6-protonated product was formed, in contrast to the results for the sodium methoxide catalyzed reaction in methanol. The reason for this is still unclear.

The air oxidation of **2b** to **4b** was also found to occur under nonprotic acid conditions. Thus, clean transformation of **2b** to **4b** occurred in chloroform at room temperature within 6–8 h. In the presence of an aqueous acid under an atmosphere of air, however, **1** was the sole product from **2b**. Again, no air oxidation product **4b** was formed under deoxygenated conditions. Recently, the formation of [4,6-*cd*]pyrazoles from the related 6β-bromo 4-en-3-one and phenylhydrazine in benzene in the presence of acetic acid has been reported.[13] When the above reaction was performed on **1**, a complex mixture of products was obtained. None of the Wharton rearrangement

(6) (a) Wharton, P. S.; Bohlem, D. H. *J. Org. Chem.* **1961**, *26*, 3615. (b) Fried, J.; Edwards, J. A. *Organic Reactions in Steroid Chemistry*; Beard, C. C., Ed.; Van Nostrand Reinhold Company: New York, 1972; p 289.

(7) Mattox, V. R.; Kendall, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 2290.

(8) Shephard, K. P. French Patent 2 487 360, 1982; *Chem. Abstr.* **1982**, *97*, 92636r.

(9) Teitelbaum, P. J.; Chu, N. I.; Cho, D.; Tökés, L.; Patterson, J. W.; Wagner, P. J.; Chaplin, M. D. *J. Pharmacol. Exp. Ther.* **1981**, *218*, 16.

(10) Holland, H. L.; Diakow, R. R. P. *Can. J. Chem.* **1979**, *57*, 1585.

(11) Rabjohn, N.; Hobert, C. A. *J. Org. Chem.* **1970**, *35*, 3240.

(12) Since the suggested ionic reaction between molecular oxygen and the dienolate contradicts the spin conservation rule, it was suggested by a referee that the reaction be done in the presence of a free radical trapping agent to substantiate the proposed mechanism. When the reaction between **2b** and sodium methoxide in toluene was carried out in the presence of 2,6-di-*tert*-butyl-4-methylphenol in the dark, complete oxidative transformation was observed, indicating that the reaction does not proceed through a radical intermediate.

(13) Ahmad, M. S.; Ansari, S. A.; Ali, M. *Ind. J. Chem.* **1985**, *24B*, 910.

product, **5**, or the keto hydrazone, **4a**, was present in the mixture. This reaction is under further investigation.

Experimental Section

The ^1H and ^{13}C NMR spectra of approximately 10% (w/v) solutions in $CDCl_3$ were obtained on a Bruker Spectrospin Model WM 300. Chemical shifts are reported in parts per million (δ scale) by employing tetramethylsilane as an internal standard. In reporting the NMR data, we have employed the following abbreviations: coupling constant in hertz (J), singlet (s), doublet (d), doublet of doublets (dd), and multiplet (m). IR spectra were recorded on a Pye-Unicam 3-200 spectrophotometer and absorptions are reported in cm^{-1}. Ultraviolet spectra were taken in methanol on a Cary spectrophotometer. Electron impact mass spectral data were obtained with Finnigan MAT CH-7 and 122-S direct inlet instrument at 10 eV. Melting points were obtained on a Thomas-Hoover capillary apparatus and are uncorrected.

Hydroxymethylenation of 16α,17α-Dihydroxy-6α-fluoro-17β-(methoxycarbonyl)androst-4-en-3-one 16,17-Acetonide. To an ice-cooled solution of **1** (1.0 g, 2.4 mmol)[14] and 10 mL of ethyl formate in 25 mL toluene under a nitrogen atmosphere was added 50% sodium hydride dispersion (1.0 g, 21 mmol) in portions, and the heterogeneous mixture was allowed to react until TLC (20% acetone–hexane) indicated complete disappearance of the starting material (15–20 min). The reaction mixture was then poured onto a mixture of 1 N HCl–ice and extracted with ethyl acetate. The ethyl acetate extract was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (12% acetone–hexane) to obtain **2a** (0.45 g, 42%) and **2b** (0.45, 42%).

16α,17α-Dihydroxy-6α-fluoro-2-(hydroxymethylene)-17β-(methoxycarbonyl)androst-4-en-3-one 16,17-acetonide (2a): mp 197–200 °C (hexane/EtOAc); UV (MeOH) 240 (ϵ 28100); IR (KBr) 3700–3300 (OH), 1730 (ester), 1640 (3-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3 H, 18-CH_3), 1.04 and 1.24 (2 s, 6 H, $C(CH_3)_2$), 1.48 (s, 3 H, 19-CH_3), 1.8–2.25 (m, 12 H), 2.38, 2.46 (2 d, 2 H, J = 12.0 Hz, 2-H), 3.80 (s, 3 H, OCH_3), 5.10 (ddd, J = 45.0, 9.0, 6.0 Hz, 6-H), 5.15 (d, 1 H, J = 5.1 Hz, 16-H), 6.19 (d, 1 H, J = 2.1 Hz, 4-H), 7.50 (br s, 1 H, C*H*–OH). Anal. Calcd for $C_{25}H_{33}FO_6$: C, 66.95, H, 7.41. Found: C, 66.66; H, 7.40.

16α,17α-Dihydroxy-6-fluoro-17β-(methoxycarbonyl)-androst-5-en-3-one 16,17-acetonide (2b): mp 147–150 °C (hexane/EtOAc); UV (MeOH) 205 (ϵ 755); IR (KBr) 1734 (ester), 1720 (3-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3 H, 18-H), 1.17, 1.24 (2 s, 6 H, $C(CH_3)_2$), 1.49 (s 3 H, 19-H), 1.09–2.55 (m, 15 H), 2.9, 3.5 (m, d, 2 H, 4-H), 3.80 (s, 3 H, OCH_3), 5.15 (d, 1 H, J = 5.2 Hz, 16-H). Anal. Calcd for $C_{24}H_{33}FO_5$: C, 68.55; H, 7.90. Found: C, 68.68; H, 8.05.

16α,17α-Dihydroxy-17β-(methoxycarbonyl)-3-(2-phenylhydrazono)androst-4-en-6-one 16,17-Acetonide (4a). A solution of **2b** (0.10 g, 0.23 mmol) and phenylhydrazine (0.05 g, 0.47 mmol) was allowed to react for 2 h in 10 mL of methanol and the solid was collected by filtration to afford **4a** (81 mg, 70%): mp 267–268 °C (hexane/EtOAc); UV (MeOH) 256 (ϵ 23500), 393 (ϵ 56000); IR (KBr) 1740 (ester), 1660 (6-C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 3 H, 18-CH_3), 1.06 (s, 3 H, 19-CH_3), 1.25, 1.49 (2 s, 6 H, $C(CH_3)_2$), 1.55–2.60 (m, 15 H), 3.81 (s, 3 H, OCH_3), 5.16 (d, 1 H, J = 4.4 Hz, 16-H), 7.08 (s, 1 H, 4-H), 7.36–6.92 (m, 5 H, Ar-H), 7.70 (s, 1 H, NH); MS, m/z 506 (M^+); HRMS, calcd for $C_{30}H_{38}N_2O_5$ (M^+) 506.2780 (found 506.2765). Anal. Calcd for $C_{30}H_{38}N_2O_5$: C, 71.12; H, 7.56; N, 5.52. Found: C, 70.79; H, 7.43; N, 5.49.

16α,17α-Dihydroxy-17β-(methoxycarbonyl)androst-4-ene-3,6-dione 16,17-Acetonide (4b). A mixture of **2b** (0.100 g, 0.23 mmol) and sodium methoxide (6.00 mg, 1.05 mmol) in 10 mL of toluene was allowed to react for 8–10 h at room temperature. The reaction was concentrated and the residue was purified by flash chromatography (15% acetone/hexane) to obtain **4b** (0.07 g, 70%): mp 196–199 °C (hexane/EtOAc); UV (MeOH) 249 (ϵ 23600); IR (KBr) 1730 (ester), 1685 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.71 (s, 3 H, 18-CH_3), 1.17, 1.49 (2 s, 6 H, $C(CH_3)_2$), 1.25 (s, 3 H, 19-CH_3), 1.53–2.73 (m, 15 H), 3.81 (s, 3 H, OCH_3), 5.16 (d, 1 H, J = 4.7 Hz, 16-H), 6.19 (s, 1 H, 4-H); HRMS, calcd for $C_{24}H_{32}O_6$ (M^+) 416.2198 (found 416.2202).

16α,17α-Dihydroxy-17β-(methoxycarbonyl)-3-(2-phenyldiazo)androsta-3,5-diene 16,17-Acetonide (5). A suspension of **1** (0.1 g, 0.23 mmol) and phenylhydrazine (0.025 g, 0.24 mmol) in methanol was allowed to react for 1 h. The solid formed was collected by filtration to obtain **5** (0.06 g, 51%): mp 218–220 °C (hexane/EtOAc); UV (MeOH) 241 (ϵ 18800), 352 (ϵ 73200); IR (KBr) 1730 (ester) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (s, 3 H, 18-CH_3), 1.01, 1.25 (2 s, 6 H, $C(CH_3)_3$), 1.55 (s, 3 H, 19-CH_3), 1.20–2.36 (m, 15 H), 2.36, (m, 1 H, 7-H axial), 2.80 (dd, 1 H, 7-H equat), 3.81 (s, 3 H, OCH_3), 5.16 (d, 1 H, J = 5.2 Hz, 16-H), 5.97 (t, 1 H, 6-H), 7.06 (s, 1 H, 4-H), 7.37–7.77 (m, 5 H, Ar-H); HRMS, calcd for $C_{30}H_{38}N_2O_4$ (M^+) 490.2831 (found 490.2831). Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.80; N, 5.71. Found: C, 73.04; H, 7.82; N, 5.57.

17β-(Methoxycarbonyl)-3,6,16α,17α-tetrahydroxyandrost-4-ene 16,17-Acetonide (7). To an ice-cooled solution of **4b** (0.15 g, 0.35 mmol) in 5 mL of methanol was added sodium borohydride (0.013 g, 0.36 mmol), and the reaction was allowed to proceed for 0.5 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic extract was washed with water and brine, dried (Na_2SO_4), and concentrated on a rotary evaporator. The residue was purified by flash chromatography (EtOAc) to obtain **7** (0.12 g, 80%): mp 174–176 °C (hexane/EtOAc); IR (KBr) 3600–3300 (OH), 1735 (ester) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (s, 3 H, 18-CH_3), 1.04 (s, 3 H, 19-CH_3), 1.23, 1.46 (2 s, 6 H, $C(CH_3)_2$), 1.20–2.11 (m, 15 H), 3.79 (s, 3 H, OCH_3), 4.20 (m, 2 H, 3,6-H) 5.13 (d, 1 H, J = 4.80 Hz, 16-H), 5.68 (s, 1 H, 4-H); HRMS, calcd for $C_{28}H_{33}O_6$ ($M - CH_3$) 405.2277 (found 405.2269).

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(14) The corresponding 17-acid was prepared as described in Kertesz and Marx (Kertesz, D. J.; Marx, M. *J. Org. Chem.* **1986**, *51*, 2315) and was converted to the methyl ester by treatment with ethereal diazomethane.